Heterocyclic Letters
Vol. 5 | No.4|609-620| Aug-Oct| 2015
ISSN : (print) 2231–3087 / (online) 2230-9632
CODEN: HLEEAI
http://heteroletters.org

PYRAZOLE-QUINOLONE-ISONIAZID HYBRIDS: SYNTHESIS, CHARACTERIZATION AND *IN VITRO* EVALUATION AS A NEW CLASS OF ANTIMICROBIAL AND ANTITUBERCULAR AGENTS.

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ABSTRACT:
A series of pyrazole-quinoline-isoniazid hybrids were designed based on molecular hybridization technique. The title compounds were synthesized via one-pot three component reaction between 3-substituted-1*H*-pyrazole-4-carbaldehydes, *N*′-(5,5-(un)substituted-3-oxocyclohex-1-enyl) isonicotinohydrazide and malononitrile or ethyl/isopropyl cyanoacetates in ethanol containing a catalytic amount of triethylamine. All derivatives were elucidated by ^{1}H NMR, ^{13}C NMR, FT-IR, elemental analysis and mass spectral data. All the newly synthesized compounds were screened for their antimicrobial and antitubercular activities.

KEY WORDS: 1*H*-pyrazole, quinolone, isoniazid, antimicrobial, antitubercular.

INTRODUCTION

From the beginning of life on the earth bacteria faces a large variety of naturally occurring antibiotics. For their existence they establish some antibiotic resistance mechanisms. That makes them resistant to most of the antimicrobial drugs, which are used from long time in clinical practice. The antibiotic resistance and multidrug resistance make bacteria as 'superbugs' and are emerging at a quick rate[I]. Additionally, more than 70% of pathogenic bacteria were expected to be resistant to at least one of the currently available antibiotics[II].
In medicinal chemistry pyrazole, quinolone and isoniazid are well known heterocycles, which individual derivatives represent the group of compounds containing excellent biological activities. Various pyrazole alkaloids like withasomnine, (*s*)-3-pyrazolylalanine, pyrazonycin shows activities such as CNS-depressant, fungicide, narcotic, antidiabetic, and antiviral metabolite. 1*H*-pyrazole derivatives were also found to possess anti-inflammatory, COX-2 inhibitors [III], analgesic [IV], antimicrobial and antioxidant activities [V]. Same way *N*-hetryl-4-substituted quinolone nucleus is a fertile source of biologically important molecules possessing various important pharmacological properties such as anticancer[VI,VII], antimicrobial activity, [VIII] antibacterial and antifungal activity [IX,X]. Isoniazid is the frontier drug which employed in the treatment of tuberculosis. Recent research has probed the mechanism of action of isoniazid, a key drug in the chemotherapy of tuberculosis and also the anti-mycobacterial potential of derivatives of isoniazid has been evaluated. From the continuous search of biologically potent drugs we conclude that, for better antimicrobial activity and to suppress antibiotic resistance, hybrid scaffolds of bio-active parent should be used. [XI-XIII] Following this hypothesis, 24 hybrids containing pyrazole-quinolone-isoniazid

nucleus have been synthesized, and in this study its showing better to good bio-activity which supports the hypothesis.

RESULTS AND DISCUSSION

CHEMISTRY

The required *N′*-(5,5-(un)substituted-3-oxocyclohex-1-enyl) isonicotinohydrazide **(3a,b)** were synthesized by nucleophilic reaction of 1,3-cyclohexanedione/dimedone **(I/II)** and isoniazid at 120°C for 30 min under solvent free condition. The title compounds **4a-x** were prepared via one-pot three component cyclocondensation reaction between aldehyde **(1a-d)**, and malononitrile or ethyl/isopropyl cyanoacetates **(2a-c)** in ethanol containing a catalytic amount of triethylamine (TEA) in excellent to good yields. (**Table 1)**

ANTIMICROBIAL SCREENING

The antimicrobial activity of synthesized compounds was carried out by broth microdilution method according to National Committee for Clinical Laboratory Standards (NCCLS)[XIV]. Anti-bacterial activity was screened against three gram-positive (*Staphylococcus aureus* MTCC 96, *Bacillus subtilis* MTCC 441, *Clostridium tetani* MTCC 449) and three gram-negative (*Escherichia coli* MTCC 443, *Salmonella typhi* MTCC 98, *Vibrio cholera* MTCC 3906) bacteria by using ampicillin and ciprofloxacin as standard antibacterial drugs. Antifungal activity was screened against two fungal species (*Candida albicans* MTCC 227 and *Trichophyton rubrum* MTCC 296) where, griseofulvin and nystatin were used as standard antifungal drugs. The antimicrobial screening data are shown in **Table 2**. All MTCC cultures were collected from Institute of Microbial Technology, Chandigarh and tested against above mentioned known drugs. Mueller Hinton broth was used as nutrient medium to grow and dilute the drug suspension for the test.

From the *in vitro* antimicrobial activity analysis it has been observed that compound **4c** (MIC = 25 µg/mL) and **4i** (MIC = 62.5 µg/mL) shows excellent activity against Gram positive bacteria *S.aureus*, while compounds **4a, 4b, 4l, 4q, 4s, 4t, 4v, 4w, 4x** (MIC = 100 µg/mL), **4k, 4r** (MIC = 125 µg/mL) shows better to good activity as comparison to ampicillin (MIC = 250 µg/mL). The compounds **4n** (MIC = 62.5 µg/mL), **4c**, **4e**, **4g**, **4i**, **4k**, **4l**, **4r** (MIC = 100 µg/mL), **4m** and **4o** (MIC = 125 µg/mL) shows excellent to good bioactivity against *C.tetani* with respect to standard drugs. While compounds **4b, 4c, 4m, 4t, 4w** (MIC = 100 µg/mL), **4d, 4i, 4l,** (MIC = 125 µg/mL) founds potent against *B.subtillis.* For the Gram negative bacteria *V. cholera* compounds **4r** (MIC = 25 µg/mL), **4s** and **4v** (MIC = 62.5 µg/mL) showed excellent activity as compared to ampicillin (MIC = 100 µg/mL). In case of inhibiting *S.typhi*, compounds **4c** (MIC = 62.5 µg/mL) were found to be potent then ampicillin (MIC = 100 µg/mL). Towards *E. coli*, compounds **4i** and **4r** (MIC = 50 µg/mL), while **4c, 4k** and **4t** (MIC = 62.5 µg/mL) have shown outstanding inhibitory effect.

Antifungal study revealed that most of all the synthesized derivatives have very good activity against *C.albicans*. The compounds **4d, 4f, 4i, 4o, 4r, 4u, 4v** and **4x** (MIC = 250 µg/mL) shows excellent potency toward *C.albicans* on comparison with standard fungicidal griseofulvin (MIC = 500 µg/mL). Unfortunately none of the synthesized derivatives shows good activity against *T.rubrum*.

ANTITUBERCULOSIS ACTIVITY

In vitro antituberculosis activity of all the newly synthesized compounds against *M. tuberculosis* H37Rv strain was determined by using Lowensteine Jensenslope method [XV-XVIII]

and the observed results are presented in **Table 2** in the form of % inhibition, relative to that of standard antitubercular drugs isoniazid. Compounds effecting less than 90% inhibition in the primary screen were not evaluated further. Compounds demonstrating at least 90% inhibition in the primary screen were re-tested at lower concentration (MIC) in a Lowensteine Jensen medium and evaluated for their MIC values. Of the compounds studied, six compounds those exhibited highest % inhibition, were again screened to get their MIC values.

Against *M. tuberculosis* compound **4r** having 96% of inhibition at 250 µg/mL and shows excellent value of MIC =12.5 µg/mL. The compound **4r** founds to be most active member against *M tuberculosis* among the series. While compounds **4c, 4v** and **4s** shows MIC = 50 µg/mL, these compounds shows inhibition of 94%, 93% and 94% respectively. The compound **4t, 4i** and **4k** represents good to moderate activity having MIC value 62.5, 62.5 and 100 µg/mL with inhibition of 92%, 91% and 90% respectively.

EXPERIMENTAL SECTION

All the reagents and solvents were obtained commercially and used without further purification. All melting points were taken in open capillaries and are uncorrected. For monitoring the progress of all reactions, purity and homogeneity of the synthesized compounds thin-layer chromatography (TLC, on aluminium plates precoated with silica gel, $60F_{254}$, Merck, Darmstadt, Germany) was used; eluent chloroform: methanol (9:1). UV radiation and/or iodine were used as the visualizing agents. The IR spectra were recorded on a Perkin-Elmer Spectrum GX FT-IR Spectrophotometer (Perkin-Elmer, USA) and only the characteristic peaks are reported in cm^{-1}. Elemental analysis (% C, H, N) was carried out by Perkin-Elmer 2400 series-II elemental analyzer (Perkin-Elmer, USA) and all compounds are within ± 0.4% of theory specified. ^{1}H NMR and ^{13}C NMR spectra were recorded in solvent DMSO-d_6 on a Bruker Advance 400F (MHz) spectrometer (Bruker Scientific Corporation Ltd., Switzerland) using TMS as an internal standard at 400 MHz and 100 MHz Chemical shifts are reported in parts per million (ppm) respectively. Mass spectra were scanned on a Shimadzu LCMS 2010 spectrometer (Shimadzu, Tokyo, Japan)

General procedure for preparation *N′*-(5,5-un(sub)-3-oxocyclohex-1-enyl) isonicotinohydrazide (3a,b)

In a round bottom flask, equimolar (3 mmol) mixture of 1,3-cyclohexanedione/dimedone, and isoniazid heated at 120°C till the completion of the reaction as confirmed by the TLC (30 min.). The crude products obtained were purified by recrystalization with ethanol:water (1:4) mixture and dried. The products were obtained quantitatively with an excellent purity.

General procedure for preparation of titled compounds 4a-x

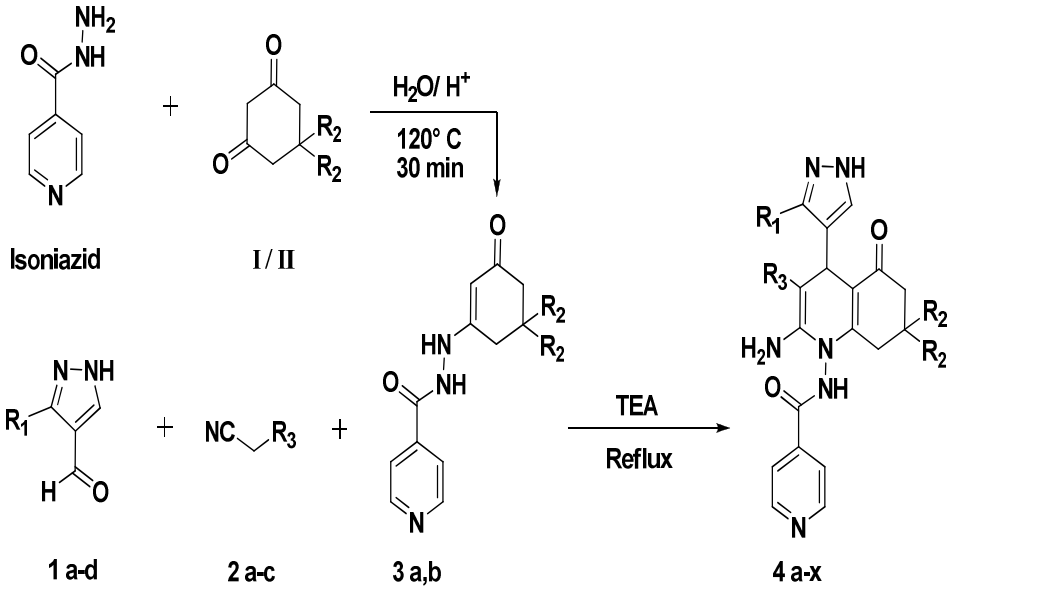
A ethanolic mixture of 3-substituted phenyl-1*H*-pyrazol-4-carbaldehyde **(1a-d)** and **2a-c** is stirred at 60°C for 5 minute in presence of catalytical amount of TEA, then *N′*-(5,5-un(sub)-3-oxocyclohex-1-enyl) isonicotinohydrazide **(3a,b)** is added and mixture is allowed to reflux for 1.5 h. After the completion of reaction (checked by TLC, eluent chloroform: methanol: 9:1) reaction mass allow to cool. Solid separated out collected by filtration and allowed for purification and recrystalization. Then pure product is used for characterization and biological assay.

In FT-IR spectra, an absorption bands around 1648-1659 and 1690-1697 cm^{-1} exhibited for -C=O stretching. The absorption bands for compounds contain -C≡N group were observed in the range of 2160-2183 cm^{-1} corresponding to C≡N stretching. The characteristic absorption

bands for all the compounds were observed in the range of 3390-3399 and 3280-3289 cm^{-1} corresponding to asymmetrical and symmetrical stretching of NH_2 group. In ^1H NMR spectra of compounds **4a-x**, a sharp singlet peak of methine proton (H4) was appeared around δ 4.48-5.54 ppm. A signal observed around δ 32.38-35.53 ppm was indicated methine carbon (C4) in ^{13}C NMR spectra of compounds **4a-x** which confirm the formation of quinolone ring. A peak around δ 11.7- 11.49 was attributed to –NH proton of amide linkage. In ^{13}C NMR spectra, the signals around δ 164.77-196.81 were arise for the carbonyl carbon (–C=O) of amide linkage, ester and cyclohexenone ring. The obtained elemental analysis values are in consonance with theoretical data. Mass spectra of title compounds showed expected molecular ion peak M^+ corresponding with proposed molecular mass. Physical, analytical and spectroscopic characterization data of the compounds **4a-x** are given then after.

Table 1 Physical data and elemental analysis of compound 4a-x

Entry	R_1	R_2	R_3	Chemical formula	Elemental analysis calc.%, (found %)			Yield %
					C	H	N	
4a	H	H	CN	$C_{25}H_{21}N_7O_2$	66.51, (66.34)	4.69, (4.57)	21.72, (22.01)	78
4b	H	H	COOEt	$C_{27}H_{26}N_6O_4$	65.05, (65.33)	5.26, (5.14)	16.86, (16.57)	87
4c	H	H	COO*i*Pr	$C_{28}H_{28}N_6O_4$	65.61, (65.39)	5.51, (5.32)	16.40,(16.78)	79
4d	H	CH_3	CN	$C_{27}H_{25}N_7O_2$	67.63, (67.79)	5.25, (5.61)	20.45, (20.59)	82
4e	H	CH_3	COOEt	$C_{29}H_{30}N_6O_4$	66.14, (65.85)	5.74, (6.11)	15.96, (16.29)	73
4f	H	CH_3	COO*i*Pr	$C_{30}H_{32}N_6O_4$	66.65, (66.37)	5.97, (6.32)	15.55, (15.42)	78
4g	F	H	CN	$C_{25}H_{20}FN_7O_2$	63.96, (64.29)	4.29, (3.96)	20.88, (20.70)	80
4h	F	H	COOEt	$C_{27}H_{25}FN_6O_4$	62.78, (63.04)	4.88, (5.18)	16.27, (16.58)	82
4i	F	H	COO*i*Pr	$C_{28}H_{27}FN_6O_4$	63.39, (63.55)	5.13, (4.82)	15.84, (16.13)	79
4j	F	CH_3	CN	$C_{27}H_{24}FN_7O_2$	65.18, (64.86)	4.86, (5.19)	19.71, (19.63)	85
4k	F	CH_3	COOEt	$C_{29}H_{29}FN_6O_4$	63.96, (64.27)	5.37, (5.13)	15.43, (15.58)	89
4l	F	CH_3	COO*i*Pr	$C_{30}H_{31}FN_6O_4$	64.50, (64.34)	5.59, (5.83)	15.04, (14.76)	72
4m	Cl	H	CN	$C_{25}H_{20}ClN_7O_2$	61.79, (62.02)	4.15, (4.08)	20.18, (20.29)	76
4n	Cl	H	COOEt	$C_{27}H_{25}ClN_6O_4$	60.84, (61.18)	4.73, (4.65)	15.77, (15.54)	83
4o	Cl	H	COO*i*Pr	$C_{28}H_{27}ClN_6O_4$	61.48, (61.79)	4.98, (5.31)	15.36, (15.24)	88
4p	Cl	CH_3	CN	$C_{27}H_{24}ClN_7O_2$	63.09, (62.77)	4.71, (4.36)	19.08, (19.32)	75
4q	Cl	CH_3	COOEt	$C_{29}H_{29}ClN_6O_4$	62.08, (61.89)	5.21, (5.59)	14.98, (15.21)	68
4r	Cl	CH_3	COO*i*Pr	$C_{30}H_{31}ClN_6O_4$	62.66, (62.53)	5.43, (5.37)	14.61, (14.47)	78
4s	Br	H	CN	$C_{25}H_{20}BrN_7O_2$	56.61, (56.44)	3.80, (3.93)	18.49, (18.73)	72
4t	Br	H	COOEt	$C_{27}H_{25}BrN_6O_4$	56.16, (56.36)	4.36, (4.67)	14.55, (14.46)	83
4u	Br	H	COO*i*Pr	$C_{28}H_{27}BrN_6O_4$	56.86, (56.49)	4.60, (4.48)	14.21, (13.96)	69
4v	Br	CH_3	CN	$C_{27}H_{24}BrN_7O_2$	58.07, (57.69)	4.33, (4.46)	17.56, (17.49)	88
4w	Br	CH_3	COOEt	$C_{29}H_{29}BrN_6O_4$	57.53, (57.44)	4.83, (4.68)	13.88, (14.22)	79
4x	Br	CH_3	COO*i*Pr	$C_{30}H_{31}BrN_6O_4$	58.16, (57.94)	5.04, (4.83)	13.57, (13.88)	73



Where R_1= Phenyl, 4-F-phenyl, 4-Cl-phenyl, 4-Br-phenyl R_2= H, CH_3 R_3= CN, COOEt, $COOCH(CH_3)_2$

Scheme 1: Synthetic route for titled derivatives.

Table 2: *In vitro* antimicrobial and antitubercular activity of pyrazole-quinoline-isoniazid derivatives 4a-x

Comp.	MINIMUM INHIBITION CONCENTRATION (MIC, µg/mL)								Anti tuberculosis test	
	Gram-positive bacteria			Gram-negative bacteria			Fungi		*M. tuberculosis H37Rv*	
	S.aureus	*B.subtillis*	*C.tetani*	*E.coli*	*S.typhi*	*V. cholrae*	*C.albicans*	*T.rubrum*	% Inhibition	MIC
	MTCC 96	MTCC 441	MTCC 449	MTCC 443	MTCC 98	MTCC 3906	MTCC 227	MTCC 296	(250 µg/mL)	(µg/mL)
4a	**100**	250	500	200	200	100	>1000	500	74%	-
4b	**100**	**100**	500	100	125	200	500	>1000	56%	-
4c	**25**	**100**	**100**	**62.5**	**62.5**	250	1000	>1000	94%	50
4d	500	**125**	250	100	200	250	**250**	500	71%	-
4e	250	**200**	**100**	125	200	250	500	500	62%	-
4f	250	250	250	250	200	250	**250**	500	30%	-
4g	500	250	**100**	100	250	500	1000	500	66%	-
4h	250	250	250	250	250	250	500	250	65%	-
4i	**62.5**	**125**	**100**	**50**	100	100	**250**	>1000	91%	62.5
4j	500	250	250	250	100	500	1000	250	58%	-
4k	**125**	250	**100**	**62.5**	200	100	500	250	90%	100
4l	**100**	**125**	**100**	250	200	100	500	1000	60%	-
4m	250	**100**	**125**	125	250	200	500	1000	45%	-
4n	200	500	**62.5**	250	200	200	>1000	1000	89%	-
4o	250	250	**125**	100	250	250	**250**	1000	78%	-
4p	200	250	250	250	250	200	>1000	250	81%	-
4q	**100**	200	250	100	200	100	>1000	500	88%	-
4r	**125**	250	**100**	**50**	125	**25**	**250**	1000	96%	12.5
4s	**100**	200	250	100	250	**62.5**	1000	>1000	94%	50
4t	**100**	**100**	200	**62.5**	100	100	1000	>1000	92%	62.5
4u	250	250	250	100	250	200	**250**	500	80%	-
4v	**100**	250	200	250	250	**62.5**	**250**	1000	93%	50
4w	**100**	**100**	250	250	250	100	500	>1000	54%	-
4x	**100**	**125**	100	500	500	100	**250**	1000	88%	-
Amp	250	250	250	100	100	100	-	-	-	-
Cipro	50	50	100	25	25	25	-	-	-	-
Nyst	-	-	-	-	-	-	100	100	-	-
Griseo	-	-	-	-	-	-	500	100	-	-
Isoniazid	-	-	-	-	-	-	-	-	99%	0.20

Amp. = Ampicillin, Cipro. = Ciprofloxacin, Nyst. = Nystatin, Griseo. = Griseofulvin, (-) = not tested,

_N_-(2-amino-3-cyano-5-oxo-4-(3-phenyl-1_H_-pyrazol-4-yl)-5,6,7,8-tetrahydroquinolin-1(4_H_)-yl)isonicotinamide (4a)

M.p 189°C, IR cm^{-1}: 3392-3285, (asym. and sym. str. of -NH_2) 3041 (Ar C-H str.), 3162 (C≡N str.), 1651 and 1696 (C=O str.) ; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 2.04-2.39 (m, 6H, 3×CH_2), 4.55 (s, 1H, H4), 7.22-8.28 (m, 1H, Ar-H + NH_2), 11.25 (s, 12H, NH), 12.80 (s, 1H, NH), ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 22.38, 23.74, 34.55, 37.18, 51.26, 112.98, 114.33, 119.53, 126.83, 127.21, 127.59, 127.83, 129.21, 129.63, 131.69, 132.53, 142.24, 144.53, 148.29, 149.47, 149.91, 151.48, 152.25, 166.07, 194.36; Molecular Weight: 451.481, m/z: 451.18

Ethyl 2-amino-1-(isonicotinamido)-5-oxo-4-(3-phenyl-1H-pyrazol-4-yl)-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (4b)

M.p 176-179 °C, IR cm^{-1}: 3390-3285, (asym. and sym. str. of -NH_2) 3041 (Ar C-H str.), 1653 and 1694 (C=O str.); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 0.68 (s, 3H, CH_3), 1.75-2.16 (m, 6H, 3×CH_2), 2.41-2.43 (m, 2H, CH_2), 4.91 (s, 1H, H4), 7.18-7.88 (m, 12H, Ar-H + NH_2), 11.18 (s, 1H, NH), 12.53 (s, 1H, NH), ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 20.95, 24.31, 28.41, 33.64, 37.39, 58.71, 72.83, 118.21, 124.55, 125.67, 126.28, 127.19, 128.15,128.74, 129.25, 136.44, 138.78, 142.19, 146.34, 146.87, 148.77, 149.84, 152.50, 153.49, 166.53, 168.69, 195.74; Molecular Weight: 498.53, m/z: 498.20

Isopropyl 2-amino-1-(isonicotinamido)-5-oxo-4-(3-phenyl-1_H_-pyrazol-4-yl)-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (4c)

M.p 184-186 °C, IR cm^{-1}: 3398-3283, (asym. and sym. str. of -NH_2) 3044 (Ar C-H str.), 1651 and 1697 (C=O str.); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 0.57-0.66 (s, 6H, 2×CH_3), 1.78-2.33 (m, 6H, 3×CH_2), 4.54-4.60 (m, 1H, CH), 5.10 (s, 1H, H4), 7.73-8.88 (m, 12H, Ar-H + NH_2), 11.49 (s, 1H, NH), 12.49 (s, 1H, NH), ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 21.22, 21.58, 23.74, 24.83, 33.39, 36.51, 65.18, 77.71, 115.30, 116.14, 123.47, 124.12, 126.34, 127.86, 131.55, 131.63, 135.41, 141.29, 145.34, 146.51, 148.98, 151.54, 153.64, 153.78, 160.88, 166.16, 168.88, 196.18; Molecular Weight: 512.56 m/z: 512.22

_N_-(2-amino-3-cyano-7,7-dimethyl-5-oxo-4-(3-phenyl-1_H_-pyrazol-4-yl)-5,6,7,8-tetrahydroquinolin-1(4_H_)-yl)isonicotinamide (4d)

M.p 187°C, IR cm^{-1}: 3392-3287, (asym. and sym. str. of -NH_2) 3048 (Ar C-H str.), 3182 (C≡N str.), 1648 and 1694 (C=O str.) ; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 0.83-0.92 (m, 6H, 2×CH_3), 1.96-2.20 (m, 4H, 2×CH_2), 4.52 (s, 1H, H4), 7.25-8.15 (m, 12H, Ar-H + NH_2), 11.09 (s, 1H, NH), 12.68 (s, 1H, NH), ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 24.32, 25.38, 31.54, 34.46, 38.12, 48.37, 56.11, 109.89, 114.36, 115.53, 126.36, 127.24, 127.48, 127.92, 129.18, 129.65, 130.57, 132.17, 143.81, 144.25, 148.66, 149.54, 149.89, 152.62, 152.89, 166.29, 196.37; Molecular Weight: 479.53 m/z: 479.21

Ethyl 2-amino-1-(isonicotinamido)-7,7-dimethyl-5-oxo-4-(3-phenyl-1_H_-pyrazol-4-yl)-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (4e)

M.p 193°C, IR cm^{-1}: 3390-3285, (asym. and sym. str. of -NH_2) 3044 (Ar C-H str.), 1651 and 1696 (C=O str.); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 0.76-0.89 (m, 6H, 2×CH_3), 1.09 (s, 3H, CH_3), 1.84-2.18 (m, 4H, 2×CH_2), 3.85 (m, 2H, CH_2), 4.82 (s, 12H, H4), 7.21-7.98 (m, 1H, Ar-H + NH_2), 11.14 (s, 1H, NH), 12.55(s, 1H, NH), ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 14.54, 25.43, 27.93, 31.81, 35.67, 37.12, 48.41, 55.81, 73.94, 118.36, 124.67, 125.35, 126.52, 127.29, 128.21,128.63, 129.51, 136.39, 138.64, 142.26, 146.57, 146.89, 148.47, 149.56, 152.23, 153.84, , 166.16, 186.62, 196.12; Molecular Weight: 526.59 m/z: 526.23

Isopropyl 2-amino-1-(isonicotinamido)-7,7-dimethyl-5-oxo-4-(3-phenyl-1*H*-pyrazol-4-yl)-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (4f)

M.p 177-180°C, IR cm^{-1}: 3391-3288, (asym. and sym. str. of -NH_2) 3050 (Ar C-H str.), 1656 and 1696 (C=O str.) ; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 0.55-0.62 (s, 6H, 2×CH_3), 0.77-0.85 (s, 6H, 2×CH_3), 1.83-2.16 (m, 4H, 2×CH_2), 4.60-4.68 (m, 1H, CH), 5.51 (s, 1H, H4), 7.55-8.78 (m, 12H, Ar-H + NH_2), 11.22 (s, 1H, NH), 12.48 (s, 1H, NH), ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 21.16, 21.37, 23.29, 24.71, 31.34, 35.49, 37.88, 48.31, 66.27, 75.18, 115.12, 116.72, 122.76, 124.69, 125.94, 127.58, 131.48, 131.56, 136.08, 141.67, 145.11, 145.58, 149.04, 151.61, 153.75, 153.84, 161.27, 165.32, 168.38, 196.28; Molecular Weight: 540.61 m/z: 540.25

***N*-(2-amino-3-cyano-4-(3-(4-fluorophenyl)-1*H*-pyrazol-4-yl)-5-oxo-5,6,7,8-tetrahydroquinolin-1(4*H*)-yl)isonicotinamide (4g)**

M.p 203°C, IR cm^{-1}: 3392-3287, (asym. and sym. str. of -NH_2) 3048 (Ar C-H str.), 3183 (C≡N str.),1652 and 1698 (C=O str.) ; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 2.08-2.40 (m, 6H, 3×CH_2), 4.57 (s, 1H, H4), 7.26-8.30 (m, 1H, Ar-H + NH_2), 11.21 (s, 11H, NH), 12.86 (s, 1H, NH), ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 21.41, 25.36, 34.72, 36.98, 53.22, 113.41, 114.58, 119.87, 126.61, 127.18, 127.71, 127.89, 129.21, 129.36, 131.88, 13237, 142.63, 144.84, 148.29, 149.71, 149.55, 151.25, 152.16, 165.68, 193.84; Molecular Weight: 469.47 m/z: 469.17

Ethyl 2-amino-4-(3-(4-fluorophenyl)-1*H*-pyrazol-4-yl)-1-(isonicotinamido)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (4h)

M.p 173-176°C, IR cm^{-1}: 3394-3285, (asym. and sym. str. of -NH_2) 3043 (Ar C-H str.), 1651 and 1695 (C=O str.); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 0.71 (s, 3H, CH_3), 1.78-2.18 (m, 6H, 3×CH_2), 2.46-2.47 (m, 2H, CH_2), 4.97 (s, 1H, H4), 7.19-9.12 (m, 11H, Ar-H + NH_2), 11.21 (s, 1H, NH), 12.59 (s, 1H, NH), ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 21.43, 24.74, 28.75, 34.21, 36.86, 57.73, 72.19, 117.74, 124.46, 125.36, 126.54, 127.25, 128.12,128.83, 129.38, 136.61, 138.34, 142.29, 145.13, 146.66, 148.31, 149.73, 151.87, 154.12, 165.36, 168.14, 196.51; Molecular Weight: 516.52, m/z: 516.19

Isopropyl 2-amino-4-(3-(4-fluorophenyl)-1*H*-pyrazol-4-yl)-1-(isonicotinamido)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (4i)

M.p 206°C, IR cm^{-1}: 3399-3288, (asym. and sym. str. of -NH_2) 3041 (Ar C-H str.), 1659 and 1698 (C=O str.) ; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 0.50-0.65 (s, 6H, 2×CH_3), 1.78-2.76 (m, 6H, 3×CH_2), 5.05 (s, 1H, H4), 4.56-4.63 (m, 1H, CH), 7.28-9.25 (m, 11H, Ar-H + NH_2), 11.42 (s, 1H, NH), 12.52 (s, 1H, NH), ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 21.25, 21.56, 23.76, 24.81, 34.68, 36.62, 65.15, 77.81, 115.26, 115.47, 124.13, 125.43, 126.85,127.68, 130.47, 130.55, 136.39, 142.26, 146.44, 146.95, 149.54, 152.65, 153.44, 153.55, 160.90, 165.99, 168.74, 196.12; Molecular Weight: 530.55, m/z: 530.21

***N*-(2-amino-3-cyano-4-(3-(4-fluorophenyl)-1*H*-pyrazol-4-yl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydroquinolin-1(4*H*)-yl)isonicotinamide (4j)**

M.p 201°C, IR cm^{-1}: 3398-3289, (asym. and sym. str. of -NH_2) 3041 (Ar C-H str.), 3168 (C≡N str.), 1658 and 1698 (C=O str.) ; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 0.87-0.95 (m, 6H, 2×CH_3), 1.99-2.19 (m, 4H, 2×CH_2), 4.50 (s, 1H, H4), 7.27-8.14 (m, 11H, Ar-H + NH_2), 11.09 (s, 1H, NH), 12.69 (s, 1H, NH), ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 24.66, 25.41, 31.78, 34.51, 37.88, 51.32, 52.69, 110.80, 114.66, 115.85, 126.21, 127.33, 127.54, 127.81,

129.12, 129.35, 130.89, 132.04, 143.78, 144.21, 148.29, 149.18, 149.88, 151.59, 152.87, 165.32, 195.47; Molecular Weight: 497.52, m/z: 497.20

Ethyl 2-amino-4-(3-(4-fluorophenyl)-1*H*-pyrazol-4-yl)-1-(isonicotinamido)-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (4k)

M.p 168-171°C, IR cm^{-1}: 3393-3282, (asym. and sym. str. of -NH_2) 3044 (Ar C-H str.), 1655 and 1691 (C=O str.) ; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 0.78-0.88 (m, 6H, 2×CH_3), 1.06 (s, 3H, CH_3), 1.87-2.20 (m, 4H, 2×CH_2), 3.88 (m, 2H, CH_2), 4.80 (s, 11H, H4), 7.19-7.86 (m, 1H, Ar-H + NH_2), 11.14 (s, 1H, NH), 12.57 (s, 1H, NH), ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 13.84, 25.67, 27.19, 31.36, 35.82, 36.91, 47.36, 57.06, 72.18, 117.68, 124.33, 125.57, 126.43, 127.18, 128.29,128.93, 129.27, 136.68, 138.44, 142.35, 145.12, 146.72, 148.37, 149.82, 151.16, 154.46, 165.69, 186.81, 195.91; Molecular Weight: 544.58 m/z: 544.22

Isopropyl 2-amino-4-(3-(4-fluorophenyl)-1*H*-pyrazol-4-yl)-1-(isonicotinamido)-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (4l)

M.p 193-196°C, IR cm^{-1}: 3393-3288, (asym. and sym. str. of -NH_2) 3042 (Ar C-H str.), 1650 and 1698 (C=O str.) ; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 0.48-0.60 (s, 6H, 2×CH_3), 0.79-0.90 (s, 6H, 2×CH_3), 1.84-2.18 (m, 4H, 2×CH_2), 4.58-4.66 (m, 1H, CH), 5.53 (s, 1H, H4), 7.48-8.64 (m, 11H, Ar-H + NH_2), 11.26 (s, 1H, NH), 12.48 (s, 1H, NH), ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 20.88, 21.30, 22.97, 24.78, 32.14, 35.26, 37.97, 48.05, 65.78, 75.23, 114.84, 116.63, 123.16, 124.55, 126.03, 127.69, 131.36, 131.97, 136.22, 141.57, 145.28, 146.12, 149.15, 151.95, 153.46, 153.27, 162.65, 166.03, 168.56, 196.18, Molecular Weight: 558.60, m/z: 558.24

***N*-(2-amino-4-(3-(4-chlorophenyl)-1*H*-pyrazol-4-yl)-3-cyano-5-oxo-5,6,7,8-tetrahydroquinolin-1(4*H*)-yl)isonicotinamide (4m)**

M.p 205°C, IR cm^{-1}: 3390-3286, (asym. and sym. str. of -NH_2) 3043 (Ar C-H str.), 3166 (C≡N str.), 1651 and 1694 (C=O str.) ; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 2.05-2.48 (m, 6H, 3×CH_2), 4.56 (s, 1H, H4), 7.23- 8.28 (m, 1H, Ar-H + NH_2), 11.26 (s, 11H, NH), 11.83 (s, 1H, NH), ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 20.27, 26.19, 32.38, 38.31, 53.16, 113.80, 114.66, 119.85, 126.89, 127.13, 127.69, 127.78, 129.09, 129.70, 131.73, 132.73, 142.59, 144.15, 148.20, 149.87, 149.97, 151.31, 152.67, 165.71, 194.14; Molecular Weight: 485.93, m/z: 485.14

Ethyl 2-amino-4-(3-(4-chlorophenyl)-1*H*-pyrazol-4-yl)-1-(isonicotinamido)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (4n)

M.p 171-175°C, IR cm^{-1}: 3394-3281, (asym. and sym. str. of -NH_2) 3043 (Ar C-H str.), 1656 and 1690 (C=O str.) ; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 0.69 (s, 3H, CH_3), 1.77-2.15 (m, 6H, 3×CH_2), 2.43-2.49 (m, 2H, CH_2), 4.95 (s, 1H, H4), 7.21-7.92 (m, 11H, Ar-H + NH_2), 11.14 (s, 1H, NH), 12.56 (s, 1H, NH), ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 20.53, 24.61, 28.39, 33.55, 37.73, 58.24, 72.41, 118.15, 124.36, 125.61, 126.14, 127.21, 128.09,128.80, 129.31, 136.57, 138.81, 142.93, 146.27, 146.74, 148.63, 149.55, 152.41, 154.31, 166.67, 167.92, 196.81; Molecular Weight: 532.98, m/z: 532.16

Isopropyl 2-amino-4-(3-(4-chlorophenyl)-1*H*-pyrazol-4-yl)-1-(isonicotinamido)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (4o)

M.p 184°C, IR cm^{-1}: 3391-3280, (asym. and sym. str. of -NH_2) 3048 (Ar C-H str.), 1659 and 1699 (C=O str.) ; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 0.51-0.67 (s, 6H, 2×CH_3), 1.78-

2.64 (m, 6H, 3×CH_2), 4.56-4.64 (m, 1H, CH), 5.06 (s, 1H, H4), 7.51-9.25 (m, 11H, Ar-H + NH_2), 11.42(s, 1H, NH), 12.55 (s, 1H, NH), ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 21.25, 21.54, 23.80, 24.79, 33.81, 36.59, 65.17, 78.60, 117.92, 124.12, 125.73, 126.18, 127.76, 128.37,128.57, 130.30, 136.38, 138.54, 142.19, 146.34, 146.87, 148.77, 149.54, 152.71, 153.50, 166.05, 186.72, 196.09, Molecular Weight: 547.00, m/z: 546.18

_N_-(2-amino-4-(3-(4-chlorophenyl)-1_H_-pyrazol-4-yl)-3-cyano-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydroquinolin-1(4_H_)-yl)isonicotinamide (4p)

M.p 198°C, IR cm^{-1}: 3393-3288, (asym. and sym. str. of -NH_2) 3041 (Ar C-H str.), 3161 (C≡N str.), 1655 and 1694 (C=O str.) ; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 0.85-0.95 (m, 6H, 2×CH_3), 1.98-2.20 (m, 4H, 2×CH_2), 4.48 (s, 1H, H4), 7.25-8.19 (m, 11H, Ar-H + NH_2), 11.07 (s, 1H, NH), 12.63 (s, 1H, NH), ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 23.94, 24.87, 32.41, 34.65, 38.19, 50.64,55.27, 110.37, 114.55, 115.60, 126.29, 127.18, 127.51, 127.89, 129.24, 129.84, 130.71, 132.56, 143.45, 144.74, 148.87, 149.46, 149.92, 152.47, 152.93, 164.77, 194.63; Molecular Weight: 513.98, m/z: 513.17

Ethyl 2-amino-4-(3-(4-chlorophenyl)-1_H_-pyrazol-4-yl)-1-(isonicotinamido)-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (4q)

M.p 183-186°C, IR cm^{-1}: 3390-3285, (asym. and sym. str. of -NH_2) 3044 (Ar C-H str.), 1651 and 1696 (C=O str.) ; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 0.76-0.86 (m, 6H, 2×CH_3), 1.09 (s, 3H, CH_3), 1.83-2.17 (m, 4H, 2×CH_2), 3.84 (m, 2H, CH_2), 4.82 (s, 11H, H4), 7.18-7.92 (m, 1H, Ar-H + NH_2), 11.17 (s, 1H, NH), 12.54 (s, 1H, NH), ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 14.38, 25.56, 28.31, 32.04, 35.17, 37.26, 48.83, 55.66, 73.41, 118.51, 124.33, 125.53, 126.42, 127.22, 128.39,128.87, 129.16, 136.46, 138.53, 142.81, 146.32, 146.93, 148.51, 149.46, 152.65, 154.61, 166.81, 186.43, 196.24; Molecular Weight: 561.03, m/z: 560.19

Isopropyl 2-amino-4-(3-(4-chlorophenyl)-1_H_-pyrazol-4-yl)-1-(isonicotinamido)-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (4r)

M.p 169°C, IR cm^{-1}: 3395-3288, (asym. and sym. str. of -NH_2) 3041 (Ar C-H str.), 1658 and 1695 (C=O str.) ; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 0.51-0.62 (s, 6H, 2×CH_3), 0.76-0.88 (s, 6H, 2×CH_3), 1.83-2.21 (m, 4H, 2×CH_2), 4.55-4.62 (m, 1H, CH), 5.51 (s, 1H, H4), 7.64-8.73 (m, 11H, Ar-H + NH_2), 11.23 (s, 1H, NH), 12.41 (s, 1H, NH), ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 21.08, 21.23, 23.26, 24.76, 33.54, 36.91, 37.83, 49.13, 66.95, 74.86, 114.21, 116.36, 123.24, 124.38, 126.11, 127.76, 131.24, 132.08, 136.38, 141.63, 145.76, 146.21, 149.55, 152.23, 153.14, 153.86, 162.48, 164.94, 168.31, 196.39, Molecular Weight: 575.06, m/z: 574.21

_N_-(2-amino-4-(3-(4-bromophenyl)-1_H_-pyrazol-4-yl)-3-cyano-5-oxo-5,6,7,8-tetrahydroquinolin-1(4H)-yl)isonicotinamide (4s)

M.p 205-208°C, IR cm^{-1}: 3391-3285, (asym. and sym. str. of -NH_2) 3041 (Ar C-H str.), 3165 (C≡N str.), 1651 and 1694 (C=O str.) ; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 2.07-2.41 (m, 6H, 3×CH_2), 4.58 (s, 1H, H4), 6.29-8.31 (m, 11H, Ar-H + NH_2), 11.23 (s, 1H, NH), 12.89 (s, 1H, NH), ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 21.44, 25.39, 34.87, 38.32, 53.39, 113.67, 114.35, 119.54, 126.17, 127.36, 127.71, 128.24, 129.21, 129.85, 131.57, 132.84, 142.43, 144.21, 148.86, 149.63, 150.21, 151.45, 152.86, 166.19, 194.04; Molecular Weight: 530.38, m/z: 529.09

Ethyl 2-amino-4-(3-(4-bromophenyl)-1*H*-pyrazol-4-yl)-1-(isonicotinamido)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (4t)

M.p 174-178°C, IR cm^{-1}: 3395-3284, (asym. and sym. str. of -NH_2) 3044 (Ar C-H str.), 1654 and 1697 (C=O str.) ; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 0.72 (s, 3H, CH_3), 1.79-2.20 (m, 6H, 3×CH_2), 2.47-2.51 (m, 2H, CH_2), 4.96 (s, 1H, H4), 7.19-7.96 (m, 11H, Ar-H + NH_2), 11.21 (s, 1H, NH), 12.53 (s, 1H, NH), ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 21.37, 24.52, 27.63, 34.49, 36.43, 57.63, 72.37, 118.29, 124.11, 125.39, 126.67, 127.30, 128.11,128.83, 129.17, 136.38, 138.53, 142.31, 146.52, 146.94, 148.71, 149.46, 152.53, 153.66, 166.24, 168.39, 195.77, Molecular Weight: 577.43, m/z: 576.11

Isopropyl 2-amino-4-(3-(4-bromophenyl)-1*H*-pyrazol-4-yl)-1-(isonicotinamido)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (4u)

M.p 195°C, IR cm^{-1}: 3398-3287, (asym. and sym. str. of -NH_2) 3044 (Ar C-H str.), 1652 and 1694 (C=O str.) ; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 0.49-0.68 (s, 6H, 2×CH_3), 1.95-2.73 (m, 6H, 3×CH_2), 5.11 (s, 1H, H4), 4.54-4.60 (m, 1H, CH), 7.73-8.18 (m, 11H, Ar-H + NH_2), 11.17 (s, 1H, NH), 12.47 (s, 1H, NH), ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 21.28, 21.46, 23.66, 24.93, 35.08, 36.48, 64.97, 77.53, 115.88, 116.78, 123.64, 124.54, 126.98, 127.51, 131.34, 131.51, 135.29, 141.41, 145.55, 146.86, 148.34, 151.12, 153.47, 153.14, 160.30, 166.36, 168.43, 196.21, Molecular Weight: 591.46, m/z: 592.13

***N*-(2-amino-4-(3-(4-bromophenyl)-1*H*-pyrazol-4-yl)-3-cyano-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydroquinolin-1(4*H*)-yl)isonicotinamide (4v)**

M.p 188-190°C, IR cm^{-1}: 3397-3286, (asym. and sym. str. of -NH_2) 3041 (Ar C-H str.), 3181 (C≡N str.), 1654 and 1697 (C=O str.) ; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 0.88-0.96 (m, 6H, 2×CH_3), 1.99-2.22 (m, 4H, 2×CH_2), 4.52 (s, 1H, H4), 7.28-8.23 (m, 11H, Ar-H + NH_2), 11.12 (s, 1H, NH), 12.69 (s, 1H, NH), ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 24.18, 25.39, 32.49, 34.12, 38.22, 48.61, 56.36, 109.96, 114.43, 115.39, 126.83, 127.14, 127.36, 127.75, 129.14, 129.65, 130.75, 132.29, 143.88, 144.54, 148.69, 149.67, 149.97, 152.74, 152.96, 165.83, 195.53; Molecular Weight: 558.43, m/z: 559.12

Ethyl 2-amino-4-(3-(4-bromophenyl)-1*H*-pyrazol-4-yl)-1-(isonicotinamido)-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (4w)

M.p 171°C, IR cm^{-1}: 3390-3285, (asym. and sym. str. of -NH_2) 3044 (Ar C-H str.), 1651 and 1696 (C=O str.) ; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 0.79-0.90 (m, 6H, 2×CH_3), 1.07 (s, 3H, CH_3), 1.5-2.21 (m, 4H, 2×CH_2), 3.86 (m, 2H, CH_2), 4.82 (s, 11H, H4), 7.22-7.96 (m, 1H, Ar-H + NH_2), 11.15 (s, 1H, NH), 12.59 (s, 1H, NH), ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 13.46, 25.52, 27.45, 31.39, 35.19, 36.37, 47.96, 57.36, 72.64, 118.64, 124.35, 125.47, 126.73, 127.93, 128.26,128.90, 129.19, 136.41, 138.56, 142.27, 146.61, 146.90, 148.68, 149.37, 152.15, 153.29, 165.87, 185.96, 196.13, Molecular Weight: 605.48, m/z: 604.14

Isopropyl 2-amino-4-(3-(4-bromophenyl)-1*H*-pyrazol-4-yl)-1-(isonicotinamido)-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (4x)

M.p 189-192°C, IR cm^{-1}: 3390-3286, (asym. and sym. str. of -NH_2) 3043 (Ar C-H str.), 1651 and 1694 (C=O str.) ; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 0.53-0.60 (s, 6H, 2×CH_3), 0.76-0.86 (s, 6H, 2×CH_3), 1.85-2.19 (m, 4H, 2×CH_2), 4.59-4.65 (m, 1H, CH), 5.54 (s, 1H, H4), 7.51-8.80 (m, 11H, Ar-H + NH_2), 11.19 (s, 1H, NH), 12.46 (s, 1H, NH) ^{13}C NMR (100 MHz, DMSO-d_6) δ ppm: 21.14, 21.39, 23.47, 24.86, 32.96, 35.53, 37.76, 48.63, 66.36, 75.36, 115.30, 116.23, 122.84, 124.57, 125.37, 127.17, 131.12, 131.86, 136.19, 141.78, 145.69,

145.96, 149.18, 151.43, 153.81, 153.97, 161.58, 166.13, 167.84, 195.96, Molecular Weight: 619.51, m/z: 618.16

CONCLUSION

The present study opens up a scope for the area which deals with isoniazid incorporating derivatives and diversity on quinoline-pyrazole nucleus, for aiming their potent antimicrobial and antitubercular activities. Some magnificent results have been obtained with the hybridized scaffold. The compounds **4c, 4r, 4i, 4s, 4v, 4k, 4t, 4n 4d, 4f, 4o, 4u** and **4x** were found to be most efficient antimicrobials and compounds **4r, 4c,4v** and **4s** were found to be most efficient antituberculars of the series. These results verify a proposed hypothesis of the present work. Furthermore, this work contributes to validate the choice of the scaffold, as a template, useful to design new antimicrobial and antitubercular compounds.

ACKNOWLEDGEMENTS

The authors are thankful to Head, Department of Chemistry, Sardar Patel University for providing ^{1}H NMR and ^{13}C NMR spectroscopy, FT-IR and research facilities. We are also thankful to CIST, Sardar Patel University for providing mass spectrometry facilities, SICART, Vallabh Vidyanagar, for elemental analysis and Microcare Laboratory, Surat, for antimicrobial screening of the compounds reported herein. One of the authors (Nileshkumar D. Vala) is grateful to UGC, New Delhi for BSR Research Fellowship.

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Received on October 2, 2015.