Heterocyclic Letters
Vol. 10| No.4|641-644|Aug-Oct |2020
ISSN : (print) 2231–3087 / (online) 2230-9632
CODEN: HLEEAI
http://heteroletters.org

A FACILE SYNTHESIS OF (3-(7-(BENZO[D]OXAZOL-2-YL)-3-HYDROXYQUINOXALIN-2-YL)-5-MERCAPTO-4H-1,2,4-TRIAZOL-4-YL)(ARYL)METHANONE DERIVATIVES

Rajeshwari Madipelly

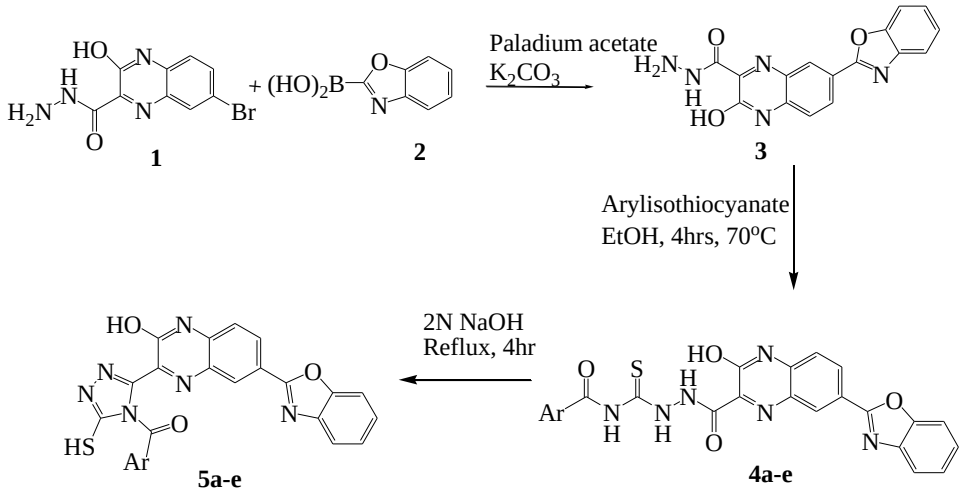
Telangana University Dichpally, Nizamabad, Telangana 503322
Email: rajeshwarimadipelly79@gmail.com

Abstract
A general and efficient method for the preparation of (3-(7-(benzo[d]oxazol-2-yl)-3-hydroxyquinoxalin-2-yl)-5-mercapto-4H-1,2,4-triazol-4-yl)(aryl)methanone derivatives has been developed via three simple steps. All the compounds synthesized were characterized by spectral analysis.

Introduction
Triazole derivatives are the promising heterocycles in the field of medicine. Their pharmacological activities are texted for antibacterial[i], antifungal[ii], antiviral[iii], anticonvulsant[iv], antiinflammatory[v] activities. Many studies have been carried out on heterocyclic systems bearing an alkylsulfanyl group as a pharmacophore[vi-viii]. Various heterocyclic rings were taken as a basis to constitute a large series of compounds. Agents with higher activity were recorded among quinoxaline, purine, benzimidazole, benzoxazole, benzothiazole, pyridine and triazole derivatives[ix-xviii]. Special attention was paid to their alkylsulfanyl derivatives. QSAR calculations carried out on various types of heterocycles proved that activity is enhanced by electron withdrawing substituents so that the alkylsulfanyl group bound to an electron deficient carbon atom in various heterocycles is responsible for antimycobacterial activity. In view of importance of triazoles, I aimed at the synthesis the title compounds.

Experimental Section
Thin layer chromatography was run on silicagel-G and visualization were done using UV light or iodine. ^{1}H NMR were recorded with a Varian Mercury plus 400 MHz instrument in DMSO-d_6 solvent using trimethylsilane as internal standard. All the chemical shifts were reported in δ (ppm) using TMS as an internal standard. The ^{1}H NMR chemical shifts and coupling constants were determined assuming first-order behavior. Multiplicity is indicated by one or more of the following: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad). Jeol-JMS D-300 spectrometer was used to record mass spectra.

Scheme



R = H, 4-chloro, 3-nitro, 4-nitro, 3-hydroxy

Result and Discussion

7-bromo-3-hydroxyquinoxaline-2-carbohydrazide (**1**) and benzo[d]oxaazol-2-ylboronic acid (**2**) react each other in presence of potassium carbonate to form 7-(benzo[d]oxazol-2-yl)-3-hydroxyquinoxaline-2-carbohydrazide **(3)**, which on reaction with different aryl isothiocyanate, results in formation of *N*-(2-(7-(benzo[d]oxazol-2-yl)-3-hydroxyquinoxaline-2-carbonyl)hydrazinecarbonothioyl)arylamides **(4a-e)**. Finally, these compounds are cyclized using NaOH to produce title compounds (**5a-e**)

7-(benzo[d]oxazol-2-yl)-3-hydroxyquinoxaline-2-carbohydrazide (3)

To a solution of 7-bromo-3-hydroxyquinoxaline-2-carbohydrazide (0.1 mol), benzo[d]oxaazol-2-ylboronic acid (0.115 mol), potassium carbonate (0.31 mol) in benzene (10 mL) and water (200 L) under nitrogen atmosphere was added palladium acetate (0.447 mol). The mixture was heated to 100°C for 3 h and then cooled to room temperature. Water (10 mL) was added and the mixture extracted with EtOAc (2×15 mL), the combined organics were washed with brine (10 mL), dried over $MgSO_4$ and concentrated in vacuo. Purification by column chromatography (10% EtOAc in hexanes) afforded the desired compound.

^{1}H NMR (400 MHz, DMSO-d_6): 9.19 (brs, 1H), 8.58 (s, 1H), 8.43 (d, 2H, J= 8.2 Hz), 8.22 (s, 1H), 8.21 (d, 2H, J = 8.2 Hz) 7.90 (m, 2H), 6.84 (brs, 2H). MS: m/z 322 $[M+H]^+$.

N-(2-(7-(benzo[d]oxazol-2-yl)-3-hydroxyquinoxaline-2-carbonyl)hydrazinecarbonothioyl)arylamides (4a-e)

The acid hydrazide (0.1 mol) and corresponding aryl isothiocyanate (0.1 mol) were refluxed in methanol (80 mL) for 4 hrs. The excess methanol was removed under pressure, cooled and the separated solid filtered and recrystalised.

N-(2-(7-(benzo[d]oxazol-2-yl)-3-hydroxyquinoxaline-2-carbonyl)hydrazinecarbonothioyl)benzamide (4a)

^{1}H NMR (400 MHz, DMSO-d_6): 9.20 (brs, 1H), 8.68 (brs, 1H), 8.44 (s, 1H), 8.24 (d, 2H, J= 8.2 Hz), 8.03 (s, 1H), 7.87 (m, 2H), 7.68 (m, 2H), 7.42 (m, 5H), 6.88 (brs, 1H). MS: m/z 485 $[M+H]^+$.

***N*-(2-(7-(benzo[d]oxazol-2-yl)-3-hydroxyquinoxaline-2-carbonyl)hydrazinecarbonothioyl)4-chlorobenzamide (4b)**

^{1}H NMR (400 MHz, DMSO-d_6): 9.18 (brs, 1H), 8.71 (brs, 1H), 8.43 (s, 1H), 8.19 (d, 2H, J= 8.2 Hz), 8.02 (s, 1H), 7.94 (m, 2H), 7.76 (d, 2H, J = 8.0 Hz), 7.43 (m, 4H), 6.86 (brs, 1H). MS: m/z 519 $[M+H]^+$.

***N*-(2-(7-(benzo[d]oxazol-2-yl)-3-hydroxyquinoxaline-2-carbonyl)hydrazinecarbonothioyl)3-nitrobenzamide (4c)**

^{1}H NMR (400 MHz, DMSO-d_6): 9.18 (brs, 1H), 8.63 (brs, 1H), 8.40 (s, 1H), 8.21 (d, 2H, J= 7.8 Hz), 7.96 (s, 1H), 7.85 (m, 2H), 7.65 (d, 2H, J = 7.8 Hz), 7.41 (m, 4H), 6.84 (brs, 1H). MS: m/z 530 $[M+H]^+$.

***N*-(2-(7-(benzo[d]oxazol-2-yl)-3-hydroxyquinoxaline-2-carbonyl)hydrazinecarbonothioyl)4-nitrobenzamide (4d)**

^{1}H NMR (400 MHz, DMSO-d_6): 9.20 (brs, 1H), 8.68 (brs, 1H), 8.46 (s, 1H), 8.20 (d, 2H, J= 7.8 Hz), 7.96 (s, 1H), 7.88 (m, 2H), 7.66 (d, 2H, J = 7.8 Hz), 7.40 (m, 4H), 6.98 (brs, 1H). MS: m/z 530 $[M+H]^+$.

***N*-(2-(7-(benzo[d]oxazol-2-yl)-3-hydroxyquinoxaline-2-carbonyl)hydrazinecarbonothioyl)3-hydroxybenzamide (4e)**

^{1}H NMR (400 MHz, DMSO-d_6): 9.48 (brs, 1H), 9.20 (brs, 1H), 8.63 (brs, 1H), 8.42 (s, 1H), 8.26 (d, 2H, J= 8.0 Hz), 7.98 (s, 1H), 7.86 (m, 2H), 7.76 (d, 2H, J = 8.0 Hz), 7.41 (m, 4H), 7.00 (brs, 1H). MS: m/z 501 $[M+H]^+$.

(3-(7-(benzo[d]oxazol-2-yl)-3-hydroxyquinoxalin-2-yl)-5-mercapto-4*H*-1,2,4-triazol-4-yl)(aryl)methanones (5a-e)

To corresponding thiosemicarbazide (0.014 mol), a solution of NaOH 2N (10 mL) was added. The reaction mixture was heated under reflux at 70 °C for four hours and then a solution of HCl 1N was added until it reached pH 4.5 when a solid product was formed. The rough product was separated and dried under vacuum at 55-60ºC and then it was recrystallized from ethanol.

(3-(7-(benzo[d]oxazol-2-yl)-3-hydroxyquinoxalin-2-yl)-5-mercapto-4*H*-1,2,4-triazol-4-yl)(phenyl)methanone (5a)

^{1}H NMR (400 MHz, DMSO-d_6): 9.33 (brs, 1H), 9.01 (brs, 1H), 8.42 (s, 1H), 8.23 (d, 2H, J = 8.0 Hz), 8.01 (d, 2H), 7.81 (m, 2H), 7.57 (m, 5H). MS: m/z 483 $[M+H]^+$.

(3-(7-(benzo[d]oxazol-2-yl)-3-hydroxyquinoxalin-2-yl)-5-mercapto-4*H*-1,2,4-triazol-4-yl)(4-chlorophenyl)methanone (5b)

^{1}H NMR (400 MHz, DMSO-d_6): 9.42 (brs, 1H), 9.05 (brs, 1H), 8.41 (s, 1H), 8.21 (d, 2H, J = 8.0 Hz), 8.02 (d, 2H), 7.83 (m, 2H), 7.56 (m, 4H). MS: m/z 517 $[M+H]^+$.

(3-(7-(benzo[d]oxazol-2-yl)-3-hydroxyquinoxalin-2-yl)-5-mercapto-4*H*-1,2,4-triazol-4-yl)(3-nitrophenyl)methanone (5c)

^{1}H NMR (400 MHz, DMSO-d_6): 9.41 (brs, 1H), 9.03 (brs, 1H), 8.41 (s, 1H), 8.25 (d, 2H, J = 7.8 Hz), 8.01 (m, 2H), 7.82 (m, 2H), 7.63 (m, 4H). MS: m/z 528 $[M+H]^+$.

(3-(7-(benzo[d]oxazol-2-yl)-3-hydroxyquinoxalin-2-yl)-5-mercapto-4*H*-1,2,4-triazol-4-yl)(4-nitrophenyl)methanone (5d)

^{1}H NMR (400 MHz, DMSO-d_6): 9.40 (brs, 1H), 9.06 (brs, 1H), 8.42 (s, 1H), 8.26 (d, 2H, J = 7.8 Hz), 8.02 (m, 2H), 7.83 (m, 2H), 7.63 (m, 4H). MS: m/z 528 $[M+H]^+$.

(3-(7-(benzo[d]oxazol-2-yl)-3-hydroxyquinoxalin-2-yl)-5-mercapto-4*H*-1,2,4-triazol-4-yl)(3-hydroxyphenyl)methanone (5e)

^{1}H NMR (400 MHz, DMSO-d_6): 9.77 (brs, 1H), 9.44 (brs, 1H), 9.11 (brs, 1H), 8.42 (s, 1H), 8.27 (d, 2H, J = 7.8 Hz), 8.03 (m, 2H), 7.79 (m, 2H), 7.56 (m, 4H). MS: m/z 499 $[M+H]^+$.

References

i. A. N. Syed, M. Gurumurthy, J. C. Swarup, P. Debashisha, J of Adv Pharm Res, 1, 26 (2010).
ii. J. Zhong, H. Aihong, L. Tao, H. Yan, L. Jianbing, F. Jianxin, J Organometallic Chem., 690, 1226 (2005).
iii. P. Elzbieta, K. Iwona, IlFarmaco, 58, 423 (2003).
iv. S. Nadeem, A. Waquar. Eur. J. Med. Chem., 45, 1536 (2010).
v. M. A. Ashraf, M. Hamdy, R. Abdel, S. A. Gamal-Eldien, A. E. Mahamoud. Eur. J. Med. Chem., 44, 117 (2009).
vi. K. Waisser, J. Hladuvkova, A. Hrabalek, V. Klimesova, L. Kubicova, J. Kunes, K. Palat, M. Machacek, J. Vinsova, V. Buchta, P. Jilek, Z. Odlerova. Folia. Pharm. Univ. Carol., 21, 69 (1998).
vii. V. Klimesova, J. Koci, L. Zahajska, Ces. Slov. Farm., 51, 26 (2002).
viii. V Klimesova, L. Zahajska, K. Waisser, J. Kaustova, U. Mollman, Farmaco., 59, 279 (2004).
ix. J. Kunes, M. Spulak, K. Waisser, M. Slosarak, J. Janota. Pharmazie., 55, 858 (2000).
x. A. Scozzafava, A. Mastrolorenzo, C. T. Supuran, Bioorg Med Chem Lett, 11, 1675 (2002).
xi. V. Klimesova, J. Kocı, M. Pour, J. Stachel, K. Waisser, J. Kaustova. Eur. J. Med. Chem., 37, 409 (2002).
xii. V. Klimesova, J. Kocı, K. Waisser, J. Kaustova. Farmaco., 57, 259 (2002).
xiii. J. Kocı, V. Klimesova, K. Waisser, J. Kaustova, H. M. Dahse, U. Mollman, Bioorg. Med. Chem. Lett., 12, 3275 (2002).
xiv. V. Klimesova, M. Svoboda, K. Waisser, M. Pour, J. Kaustova. Farmaco., 54, 666 (1999).
xv. V. Klimesova, M. Svoboda, K. Waisser, J. Kaustova, V. Buchta, K. Kralova, Eur. J. Med. Chem., 34, 433 (1999)
xvi. V. Klimesova, M. Svoboda, K. Waisser, M. Machacek, V. Buchta, Z. Odlerova. Arch. Pharm. (Pharm. Med. Chem.), 29, 438 (1996).
xvii. I. Mir, M. T. Siddiqui, Tetrahedron., 26, 5235 (1970).
xviii. N. N. Gulerman, H. N. Dogan, S. Rollas, C. C. Johansson¸ C. elik, Farmaco., 56, 953 (2001).

Received on July 30, 2020.