



Microwave Assisted Synthesis of 3-Chloro-N-(2-(5-chloro-1-tosyl-1H-benzo [d] Imidazol-2-yl) ethyl)-N-Substituted Quinoxalin-2-Amine Derivatives Using DCQX

K.Shashikala^{1*}, E.Laxminarayana², M.Ramesh³, M.Thirumala Chary⁴

¹ Geethanjali College of Engineering and Technology, Cheeryal(V), Keesara(M), Medchal Dt 501301, Telangana, India

² Sreenidhi Institute of Science and Technology (Autonomous), Ghatkesar, Hyderabad 501301, Telangana, India

³ Department of Biotechnology, Jawaharlal Nehru Technological University Kakinada, East Godavari Dt, Andhrapradesh 533003, India

⁴ Jawaharlal Nehru Technological University Hyderabad, Kukatpally, Hyderabad 500085, Telangana, India

E-mail: kala.shashi2010@gmail.com

Abstract: The microwave assisted synthesis of 3-Chloro-N-(2-(5-chloro-1-tosyl-1H-benzo [d] imidazol-2-yl) ethyl)-N-substituted quinoxalin-2-amine derivatives is described. 2,3-dichloro quinoxaline (DCQX), as a starting compound and propargyl bromide, as an efficient alkylating agent are used in the synthesis of N-substituted quinoxalin-2-amine derivatives. We realized that microwave assisted synthesis is efficiently replacing conventional method of synthesis.

Keywords: 2,3-dichloroquinoxaline, quinoxaline, imidazoles, alkylating agent, microwave assisted synthesis

1. Introduction

There are several reported methods for the synthesis of quinoxaline-2-amine derivatives. Nevertheless, synthesis using 2,3-dichloroquinoxaline (DCQX) with nucleophilic species such as aryl amine has become a feasible substitute because of the presence of two chlorine atoms at C2 and C3 of DCQX. 2,3-dichloroquinoxaline (DCQX) is a reagent, extensively used as a synthetic intermediate in pharmaceutical industry as well as materials science^[1,2]. Furthermore, this reagent is easily prepared from low-cost starting materials and commercially available.

One of the major advantages associated with the reactions of DCQX with nucleophiles is the possibility to control single or double substituted products. This exceptional feature of DCQX makes it significant in the synthesis of specific products that can be used in a variety of applications^[3-7]. Propargyl bromide, an efficient alkylating agent is used for the N-alkylation of aryl amides. It is also used in enyne metathesis of propargylic amines, propargylation of spiro ketones, synthesis of allylic alcohols and enone complexes^[8,9].

The effective approach for the synthesis of quinoxalin-2-amines is the reaction between 1,2-diamines with aldehydes and isocyanides using CeO₂ nanoparticle catalyst. Also 3,4-dihydroquinoxalin-2-amines were synthesized by reactions between 1,2-diamines, ketones and isocyanides^[10].

Reaction between 2,3-dichloro quinoxaline and anilines is a convenient method for the preparation of N-aryl substituted 3-chloroquinoxalin-2-amines, particularly, 2-(N-aryl amino)-3-chloroquinoxalines that are further converted into N-substituted 3-chloro-N-(2-(1-tosyl-1H-benzo [d]-imidazol-2-yl) ethyl) quinoxalin-2-amine^[11]. This method is facilitated by AlCl₃ on forming C-N bond^[11]. These target molecules were found to be potential inhibitors of phosphodiesterase 4 (PDE-4) and have apoptosis inducing properties in an animal model (zebrafish)^[12,13]. Further, the reaction is facilitated in more effective way using an alkylating agent, propargyl bromide.

2. Results and discussions

All the compounds were synthesized using microwave irradiation. The synthesis of new compounds is described according to synthetic Figure 1. Compound 2 was synthesized from the starting materials, 2,3-dichloroquinoxaline (DCQX) and aniline, substituted at 4th position. Then compound 2 is irradiated with an alkylating agent, propargyl bromide in presence potassium carbonate and DMF to acquire compound 3. The final compound 3-Chloro-N-(2-(5-chloro-1-tosyl-1H-benzo [d] imidazol-2-yl) ethyl)-N-substituted quinoxalin-2-amine (4) is obtained, when compound 3 was reacted with a

mixture containing TSN_3 , CuI , Et_3N and CH_3CN .

The structures of all the synthesized compounds were confirmed by $^1\text{H-NMR}$, $^{13}\text{C-NMR}$ and Mass spectral data. A triplet at 4.51-4.56 ppm represents CH_2N group. A peak in the range of 3.61-4.73 ppm indicates the presence of methylene group. Aromatic protons were observed in expected regions in the range of 7-8 ppm. The $[\text{M} + \text{H}]$ peaks of mass spectra of compounds are in agreement with their molecular formula.

3. Experimental section

All the chemicals used were purchased from Sigma-aldrich, Avra Laboratories. Solvents and reagents were obtained from commercial sources. Microwave assisted synthesis was carried out in BP090 Laboratory grade microwave oven. Melting Points are uncorrected and were determined using open capillary tubes in a bath of Sulphuric acid. TLC analyses were done on Merck pre-coated Plates (silica gel 60 F254) and spotting was done using Iodine / UV lamp. $^1\text{H-NMR}$ and $^{13}\text{C-NMR}$ were recorded in CDCl_3 / DMSO-d_6 using Varian MR-400MHZ and 100MHZ spectrometer and TMS as a reference standard. Mass spectra were recorded on an Agilent-LCMS instrument.

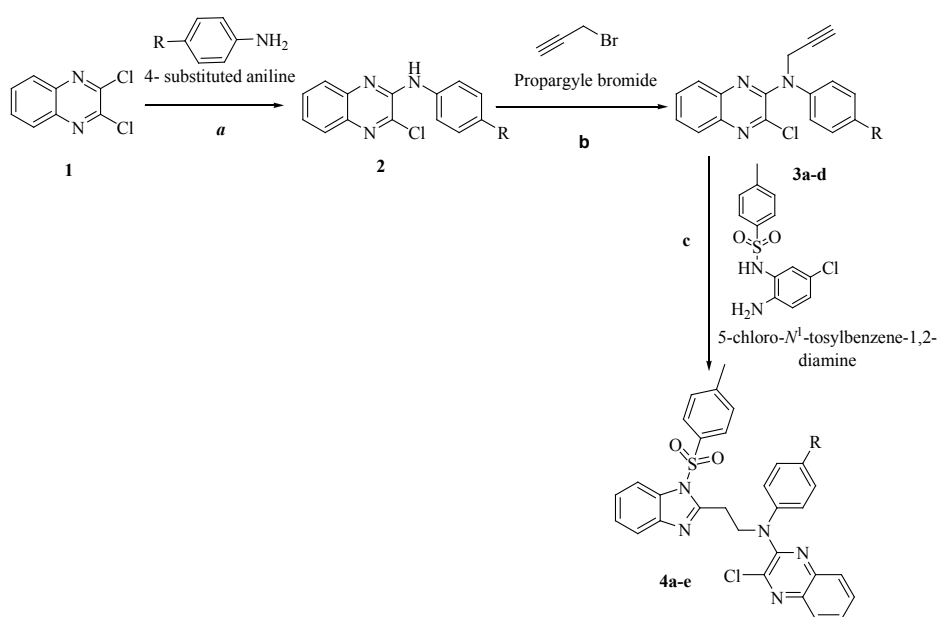


Figure 1. Synthesis of 3-Chloro-N-(2-(5-chloro-1-tosyl-1H-benzo [d] imidazol-2-yl) ethyl)-N-p-tolyl quinoxalin-2-amine (4a-e)

Reagents and Conditions: (a) $n\text{-BuOH}$; M.W., 130°C ; 30 min. (b) K_2CO_3 ; DMF ; M.W.; 110°C ; 15min. (c) TSN_3 ; CuI ; Et_3N ; CH_3CN ; M.W.; 120°C ; 20 min;

3a R = OCH_3 ; 3b R = Br; 3c R = Cl; 3d R = F

4a R = CH_3 ; 4b R = OCH_3 ; 4c R = Br; 4d R = Cl; 4e R = F

Step 1: Synthesis of 3-Chloro-N-(p-tolyl)-N-(prop-2-ynyl) quinoxalin-2-amine (2)

2,3-dichloroquinoxaline (1) (1mmol) and substituted aniline (1mmol) in $n\text{-BuOH}$ (2mL) was subjected to irradiation in microwave at 130°C for 30 min. Reaction mixture was allowed to cooled to room temperature solvent was evaporated in reduced pressure. Crude material was purified by crystallization using ethanol to get compound 2.

$^1\text{H-NMR}$ (400MHz CDCl_3): δ = 7.95 (d, 1H, J = 7.8 Hz, ArH), 7.88 (d, 1H, J = 7.8 Hz, ArH), 7.67 (t, 1H, ArH), 7.56 (t, 1H, ArH), 7.17 (d, 2H, J = 7.6 Hz, ArH), 7.03 (d, 2H, J = 7.6 Hz, ArH), 4.73 (d, 2H, J = 2 Hz, $-\text{CH}_2$), 2.37 (s, 3H, $-\text{CH}_3$), 2.19 (t, 1H, C H);

$^{13}\text{C-NMR}$ (100MHz, CDCl_3): δ = 149, 142, 141, 139, 138, 136, 130, 129, 127, 127, 127, 125, 79, 72, 43, 21; Mass: m / z = 308.6 $[\text{M}^+]$.

Step 2: General experimental procedure for the synthesis of (3a-d)

K_2CO_3 (0.7mmol) was added to a solution of compound 2 (0.47mmol) and propargyl bromide (80% in toluene) (0.94 mmol) in DMF (1mL) was subjected to microwave irradiation at 110°C for 15 min. After completion of reaction, reaction

mixture was diluted with water (15mL), extracted with EtOAc (3 × 8mL). The combined organic layer was washed with water (2 × 8mL), aqueous sodium chloride solution (10mL), dried over anhydrous Na₂SO₄ and concentrated. Crude material was purified by triturating with diethyl ether to get compound 3.

3-Chloro-N-(4-methoxyphenyl)-N-(prop-2-ynyl) quinoxalin-2-amine (3a)

¹H NMR (400MHz CDCl₃): δ = 7.92 (d, 1H, J = 7.8 Hz, ArH), 7.90 (d, 1H, J = 7.8 Hz, ArH), 7.67 (t, 1H, ArH), 7.54 (t, 1H, ArH), 7.09 (d, 2H, ArH), 7.09 (d, 2H, ArH), 6.90 (d, 2H, ArH), 4.69 (d, 2H, J = 2.4 Hz, -CH₂), 3.82 (s, 3H, -CH₃), 2.19 (t, 1H, -CH);

¹³C NMR (100MHz, CDCl₃): δ = 158, 149, 141, 139, 138, 138, 130, 127, 127, 127, 114, 79, 72, 72, 55, 55, 43; Mass: m/z = 325 [M⁺];

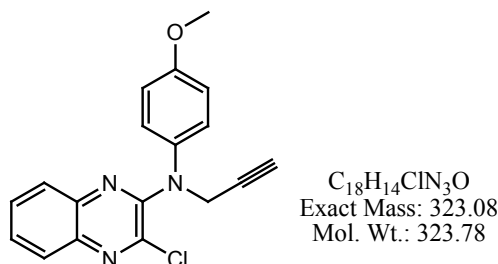


Figure 2. C₁₈H₁₄ClN₃O, exact mass: 323.08, Mol. Wt.: 323.78

3-Chloro-N-(4-bromophenyl)-N-(prop-2-ynyl) quinoxalin-2-amine (3b)

¹H NMR (400MHz CDCl₃): δ = 7.94 (d, 1H, ArH), 7.91 (d, 1H, ArH), 7.72 (t, 1H, ArH), 7.62 (t, 1H, ArH), 7.49 (d, 2H, ArH), 7.01 (d, 2H, ArH), 4.74 (d, 2H, J = 2 Hz, -CH₂), 2.21 (t, 1H, -CH);

¹³C NMR (100MHz, CDCl₃): δ = 148, 144, 141, 139, 138, 132, 131, 130, 128, 127, 127, 126, 119, 79, 72, 43; Mass: m/z = 374 [M⁺];

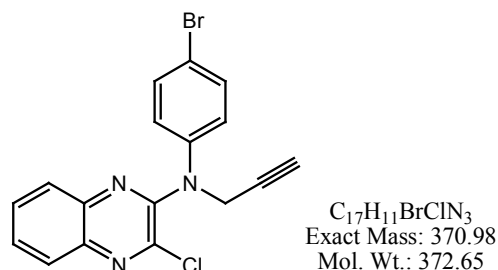


Figure 3. C₁₇H₁₁BrClN₃, exact mass: 370.98, Mol. Wt.: 372.65

3-Chloro-N-(4-chlorophenyl)-N-(prop-2-ynyl) quinoxalin-2-amine (3c)

¹H NMR (400MHz CDCl₃): δ = 7.93 (d, 1H, ArH), 7.90 (d, 1H, ArH), 7.72 (t, 1H, ArH), 7.61 (t, 1H, ArH), 7.48 (d, 2H, ArH), 7.00 (d, 2H, ArH), 4.73 (d, 2H, J = 2.2 Hz, -CH₂), 2.20 (t, 1H, -CH);

¹³C NMR (100MHz, CDCl₃): δ = 148, 144, 141, 139, 138, 132, 131, 130, 128, 127, 127, 126, 119, 79, 72, 43; Mass: m/z = 329 [M⁺];

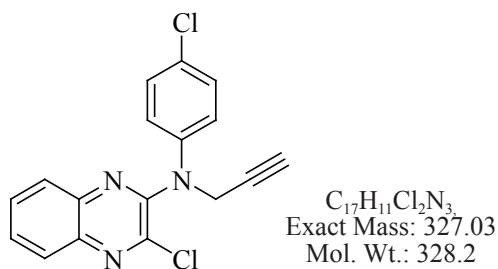


Figure 4. C₁₇H₁₁Cl₂N₃, exact mass: 327.03, Mol. Wt.: 328.2

3-Chloro-N-(4-fluorophenyl)-N-(prop-2-ynyl) quinoxalin-2-amine (3d)

$^1\text{H NMR}$ (400MHz CDCl_3): δ = 7.93 (d, 1H, ArH), 7.90 (d, 1H, ArH), 7.70 (t, 1H, ArH), 7.60 (t, 1H, ArH), 7.50 (d, 2H, ArH), 7.00 (d, 2H, ArH), 4.73 (d, 2H, J = 2 Hz, $-\text{CH}_2$), 2.20 (t, 1H, $-\text{CH}$);

$^{13}\text{C NMR}$ (100MHz, CDCl_3): δ = 149, 144, 141, 139, 138, 132, 131, 130, 128, 127, 127, 126, 119, 79, 72, 43; Mass: m/z = 313 [M^+];

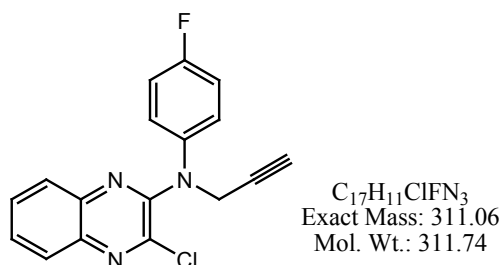


Figure 5. $\text{C}_{17}\text{H}_{11}\text{ClFN}_3$, exact mass: 311.06, Mol. Wt.: 311.74

Step 3: General experimental procedure for the synthesis of (4 a-e)

To a solution of Compound 3, reaction mixture containing, p-tolyl sulfonyl azide (0.36mmol), terminal alkyne (0.35mmol) ortho-amino aniline (0.33mmol), CuI (0.03), MeCN (1mL) and Et_3N (0.66mmol) was added at room temperature and stirred for 1h. Then, added the con. H_2SO_4 (0.1mL). The resulting reaction mixture was subjected to microwave irradiation at 120°C for 20 min. Reaction mixture was diluted with cold water, basified with K_2CO_3 and extracted with EtOAc ($3 \times 5\text{mL}$). The combined organic layer was washed with water, brine, dried over anh. Na_2SO_4 and concentrated. Crude material was purified by flash column chromatography over silica gel (100-200mesh) column chromatography using 50-70% EtOAc in pet-ether to get pure compound 4.

3-Chloro-N-(2-(5-chloro-1-tosyl-1H-benzo [d] imidazol-2-yl)ethyl)-N-p-tolylquinoxalin-2-amine (4a)

$^1\text{H NMR}$ (400MHz CDCl_3): δ = 7.87 (d, 1H, ArH), 7.84 (d, 1H, ArH), 7.79 (d, 1H, ArH), 7.65 (m, 3H, ArH), 7.62 (d, 1H, ArH), 7.55 (m, 1H, ArH), 7.14-7.01 (m, 7H, ArH), 4.56 (t, 2H, $-\text{CH}_2\text{N}$), 3.62 (t, 2H, $-\text{CH}_2$), 2.50 (s, 3H, $-\text{CH}_3$), 2.34 (s, 3H, $-\text{CH}_3$);

$^{13}\text{C NMR}$ (100MHz, CDCl_3): δ = 161, 159, 151, 149, 145, 142, 141, 139, 139, 139, 135, 135, 133, 129, 127, 127, 126, 126, 126, 125, 119, 116, 113, 52, 27, 21, 21; Mass: m/z = 604 [M^+];

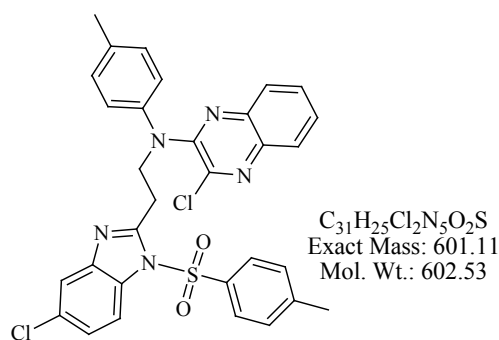


Figure 6. m/e : 601.11 (100.0%), 603.11 (69.8%), 602.11 (36.3%), 604.11 (23.8%), 605.10 (13.1%), 603.12 (5.6%), 605.11 (4.6%), 606.11 (4.6%), 604.10 (1.3%) C, 61.79; H, 4.18; Cl, 11.77; N, 11.62; O, 5.31; S, 5.32

3-Chloro-N-(2-(5-chloro-1-tosyl-1H-benzo [d] imidazol-2-yl) ethyl)-N-(4methoxy phenyl) quinoxalin-2-amine (4b)

$^1\text{H NMR}$ (400MHz CDCl_3): δ = 7.91 (d, 1H, ArH), 7.88 (d, 1H, ArH), 7.78 (d, 1H, ArH), 7.69 (m, 3H, ArH), 7.60 (d, 1H, ArH), 7.56 (m, 1H, ArH), 7.18-7.02 (m, 7H, ArH), 4.58 (t, 2H, $-\text{CH}_2\text{N}$), 3.77 (s, 3H, $-\text{CH}_3$), 3.61 (t, 2H, $-\text{CH}_2$), 2.35 (s, 3H, $-\text{CH}_3$);

$^{13}\text{C NMR}$ (100MHz, CDCl_3): δ = 161, 159, 151, 149, 145, 142, 141, 139, 139, 139, 138, 135, 134, 133, 130, 127, 127, 126, 126, 126, 125, 125, 119, 116, 113, 52, 45, 27, 21; Mass: m/z = 620 [M^+];

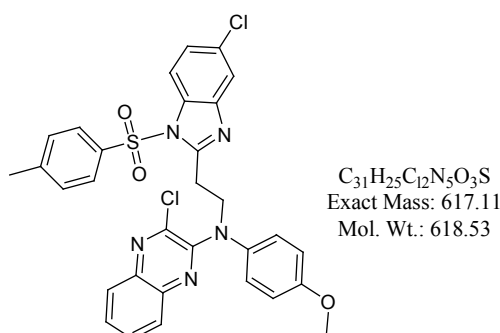


Figure 7. m/e: 617.11 (100.0%), 619.10 (68.5%), 618.11 (33.9%), 620.11 (22.1%), 621.10 (13.6%), 619.11 (7.0%), 622.10 (4.8%), 621.11 (4.4%), 620.10 (3.3%), 618.10 (2.6%) C, 60.20; H, 4.07; Cl, 11.46; N, 11.32; O, 7.76; S, 5.18

3-Chloro-N-(2-(5-chloro-1-tosyl-1H-benzo [d] imidazol-2-yl) ethyl)-N-(4-bromophenyl) quinoxalin-2-amine (4c)

^1H NMR (400MHz CDCl_3): δ = 7.95 (d, 1H, ArH), 7.91 (d, 1H, ArH), 7.79 (d, 1H, ArH), 7.70 (m, 3H, ArH), 7.65 (d, 1H, ArH), 7.58 (m, 1H, ArH), 7.49 (d, 2H, ArH), 7.20-7.01 (m, 5H, ArH), 4.56 (t, 2H, $-\text{CH}_2\text{N}$), 3.62 (t, 2H, $-\text{CH}_2$), 2.36 (s, 3H, $-\text{CH}_3$);

^{13}C NMR (100MHz, CDCl_3): δ = 160, 159, 151, 149, 145, 142, 141, 139, 139, 138, 135, 134, 133, 130, 127, 127, 126, 126, 126, 125, 125, 119, 116, 113, 52, 27, 21; Mass: m/z = 668 [M^+];

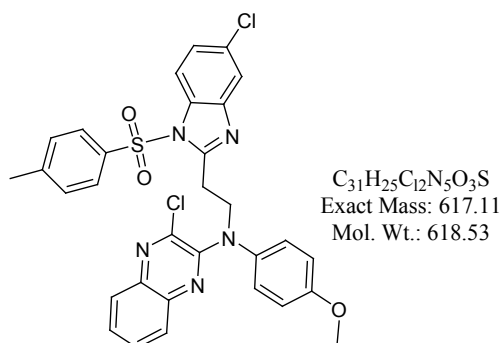


Figure 8. m/e: 617.11 (100.0%), 619.10 (68.5%), 618.11 (33.9%), 620.11 (22.1%), 621.10 (13.6%), 619.11 (7.0%), 622.10 (4.8%), 621.11 (4.4%), 620.10 (3.3%), 618.10 (2.6%) C, 60.20; H, 4.07; Cl, 11.46; N, 11.32; O, 7.76; S, 5.18

3-Chloro-N-(2-(5-chloro-1-tosyl-1H-benzo [d] imidazol-2-yl) ethyl)-N-(4-chlorophenyl) quinoxalin-2-amine (4d)

^1H NMR (400MHz CDCl_3): δ = 7.96 (d, 1H, ArH), 7.91 (d, 1H, ArH), 7.80 (d, 1H, ArH), 7.69 (m, 3H, ArH), 7.66 (d, 1H, ArH), 7.59 (m, 1H, ArH), 7.49 (d, 2H, ArH), 7.19-7.02 (m, 5H, ArH), 4.51 (t, 2H, $-\text{CH}_2\text{N}$), 3.61 (t, 2H, $-\text{CH}_2$), 2.37 (s, 3H, $-\text{CH}_3$);

^{13}C NMR (100MHz, CDCl_3): δ = 160, 159, 151, 149, 145, 142, 141, 141, 139, 139, 138, 135, 134, 133, 130, 127, 127, 126, 126, 126, 125, 125, 119, 116, 113, 52, 27, 21; Mass: m/z = 624 [M^+];

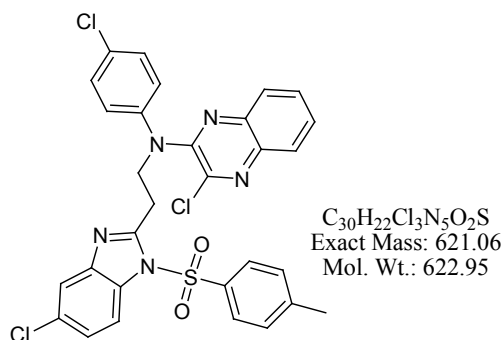


Figure 9. m/e: 623.05 (100.0%), 621.06 (99.6%), 625.05 (35.5%), 622.06 (33.4%), 624.06 (33.1%), 626.05 (12.2%), 623.06 (6.4%), 625.06 (5.9%), 627.05 (5.1%), 624.05 (2.6%), 627.06 (1.9%), 622.05 (1.8%), 628.05 (1.6%) C, 57.84; H, 3.56; Cl, 17.07; N, 11.24; O, 5.14; S, 5.15

3-Chloro-N-(2-(5-chloro-1-tosyl-1H-benzo[d]imidazol-2-yl) ethyl)-N-(4-fluorophenyl) quinoxalin-2-amine (4e)

^1H NMR (400MHz CDCl_3): δ = 7.94 (d, 1H, ArH), 7.90 (d, 1H, ArH), 7.81 (d, 1H, ArH), 7.70 (m, 3H, ArH), 7.65 (d, 1H, ArH), 7.60 (m, 1H, ArH), 7.50 (d, 2H, ArH), 7.21-7.03 (m, 5H, ArH), 4.52 (t, 2H, $-\text{CH}_2\text{N}$), 3.63 (t, 2H, $-\text{CH}_2$), 2.38 (s, 3H, $-\text{CH}_3$);

^{13}C NMR (100MHz, CDCl_3): δ = 160, 159, 151, 149, 145, 142, 141, 141, 139, 139, 138, 135, 134, 133, 130, 127, 127, 126, 126, 126, 125, 125, 119, 116, 113, 52, 27, 21; Mass: m/z = 607 [M^{+1}].

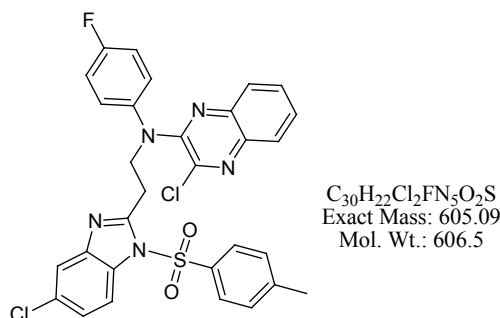


Figure 10. m/e : 605.09 (100.0%), 607.08 (68.5%), 606.09 (32.8%), 608.09 (21.3%), 609.08 (13.6%), 607.09 (6.4%), 610.08 (4.6%), 609.09 (4.0%), 608.08 (3.2%), 606.08 (2.6%) C, 59.41; H, 3.66; Cl, 11.69; F, 3.13; N, 11.55; O, 5.28; S, 5.29

4. Conclusion

Derivatives of 3-Chloro-N-(2-(5-chloro-1-tosyl-1H-benzo [d] Imidazol-2-yl) ethyl)-N-Substituted Quinoxalin-2-Amine were successfully prepared from starting material DCQX. All the synthesized compounds were characterized by ^1H NMR, ^{13}C NMR and LCMS analytical methods. Authors have succeeded in using microwave irradiation.

5. Acknowledgements

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