Supplementary Informatiomn

Chloroquinoline-acetamide hybrids: A promising series of potential antiprotozoal agent

Afreen Inam, Robyn L. Van Zyl, Natasha J. van Vuuren, Chien-Teng Chen, Fernando Avecilla, Subhash M. Agarwal , Amir Azam

Table- Bond lengths [Å] and angles [°] for 2-(4-(7-chloroquinolin-4-yl)piperazine-1-yl)-*N*-(4-fluorophenyl)acetamide (**A7**), for 2-(4-(7-chloroquinolin-4-yl)piperazine-1-yl)-*N*-*p*-tolylacetamide (**A8**)**,** for 2-(4-(7-chloroquinolin-4-yl)piperazine-1-yl)-*N*-*o*-tolylacetamide (**A 12**) and 2-(4-(7-chloroquinolin-4-yl)piperazine-1-yl)-1-(4-(2,3-dichlorophenylpipezin-1-yl)-ethanone (**A21**).

Bond lengths	**A7**	**A8**	**A12**	**A21**
Cl(1)-C(1)	1.7373(11)	1.7404(14)	1.7380(12)	1.7369(11)
Cl(2)-C(15)				1.7257(11)
Cl(3)-C(16)				1.7337(12)
F(1)-C(13)	1.3659(14)			
O(1)-C(9)	1.2212(14)	1.2160(17)	1.2207(15)	1.2255(13)
N(1)-C(5)	1.3994(14)	1.4006(18)	1.4090(14)	1.4054(13)
N(1)-C(6)	1.4613(14)	1.4732(18)	1.4605(15)	1.4655(13)
N(1)-C(21)				1.4748(13)
N(1)-C(17)	1.4751(14)	1.4589(18)	1.4696(15)	
N(2)-C(8)	1.4539(15)	1.4636(18)	1.4564(15)	1.4585(13)
N(2)-C(7)	1.4670(15)	1.4638(18)	1.4588(16)	1.4574(14)

N(2)-C(16)	1.4674(14)	1.4702(18)	1.4625(16)	
N(2)-C(20)				1.4650(13)

Angles	**A7**	**A8**	**A12**	**A21**
C(5)-N(1)-C(6)	115.86(9)	117.11(11)	115.12(10)	115.10(8)
C(5)-N(1)-C(21)				116.43(8)
C(6)-N(1)-C(21)				109.97(8)
C(5)-N(1)-C(17)	114.69(9)	116.95(11)	114.39(9)	
C(6)-N(1)-C(17)	109.46(9)	110.01(11)	110.54(9)	
C(8)-N(2)-C(7)	111.16(9)	110.38(11)	112.00(10)	110.73(8)
C(7)-N(2)-C(20)				109.43(8)
C(8)-N(2)-C(20)				112.45(9)
C(8)-N(2)-C(16)	110.26(9)	110.11(11)	111.66(10)	
C(7)-N(2)-C(16)	109.03(9)	108.47(11)	109.72(10)	

Table - Hydrogen bonds for the compounds 2-(4-(7-chloroquinolin-4-yl)piperazine-1-yl)-*N*-(4-fluorophenyl)acetamide (**A7**), 2-(4-(7-chloroquinolin-4-yl)piperazine-1-yl)-*N*-*p*-tolylacetamide (**A8**) and 2-(4-(7-chloroquinolin-4-yl)piperazine-1-yl)-*N*-*o*-tolylacetamide (**A12**) [Å and °].

A7

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O(1W)-H(1WA)...N(4)#1	0.831(9)	2.080(10)	2.8965(13)	167.5(16)
O(1W)-H(1WB)...N(2)	0.824(9)	2.137(9)	2.9461(13)	167.3(15)
N(3)-H(3)...O(1W)#2	0.86	2.03	2.8740(13)	165.1

Symmetry transformations used to generate equivalent atoms:

#1 x+1,y+1,z #2 x+1,y,z

A8

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N(3)-H(3N)...N(2)	0.870(18)	2.248(17)	2.7186(17)	113.8(14)

A12

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N(3)-H(3N)...N(2)	0.815(17)	2.165(17)	2.6662(15)	119.8(14)

Spectral data of the different sutituted chloro acetamides (1-27)

2- chloro-N- phenylacetamide (1): Yield 75%, White solid, 1HNMR (300MHz, CDCl3) δ(ppm): 8.22 (s, 1H), 7.56 (d, 2H, *J* =8.1Hz), 7.39-7.34 (m, 2H), 7.21-7.16 (m, 1H), 4.20 (s, 2H) [24]

Methyl 2-(2-chloroacetamido) benzoate (2): Yield 72%, White solid, 1HNMR (300MHz, CDCl3) δ(ppm): 11.91 (s, 1H) 8.74 (d, 1H, *J* =8.1Hz), 8.11 (d, 1H, *J* =6.6Hz), 7.62-7.574 (m, 1H), 7.21-7.16 (m, 1H), 4.24 (s, 2H) 1.74 (s, 3H) [25]

2-chloro-N-(2, 4-difluorophenyl) acetamide (3): Yield 70%, White solid, 1HNMR (300MHz, CDCl3) δ(ppm): 9.36 (s, 1H), 8.54 (m, 2H), 7.99 (s, 1H), 4.11 (s, 2H)[24].

***N*-(3-acetylphenyl)-2-chloroacetamide (4)**: Yield 71%, White solid, 1HNMR (300MHz, CDCl3) δ(ppm) : 8.40 (s, 1H) , 8.06 (s , 1H) , 7.95 (d, 1H, *J* =8.1 Hz) ,7.79 (d ,1H, *J* =7.8 Hz), 7.52 (t, 1H, *J* =7.8 Hz), 4.23 (s, 2H), 2.63 (s, 3H)[26].

***N*-(4-acetylphenyl)-2-chloroacetamide (5)**: Yield 73%, Yellow solid, H1NMR (300MHz, CDCl3) δ(ppm) : 8.40 (s, 1H) , 7.99-7.95 (m , 2H), 7.69 (d, 2H, *J* =8.7 Hz) , 4.22 (s, 2H) , 2.59 (s, 3H)[27].

2-chloro-N-(2-fluorophenyl)acetamide (6): Yield 78%, White solid,1HNMR (300MHz, CDCl3) δ(ppm): 8.55 (s, 1H) ,8.33-8.27 (m , 1H) , 7.24-7.12 (m , 3H) , 4.24 (s ,2H) [28]

2-chloro-N-(4-fluorophenyl)acetamide (7): Yield 80%, White solid,1HNMR (300MHz, CDCl3) δ(ppm) : 8.24 (s, 1H) , 7.56-7.51 (m , 2H) ,7.11-7.05 (m, 2H), 4.34 (s,2H).[28]

2-chloro-N-*p*-tolylacetamide (8): Yield 82%, White solid, 1HNMR (300MHz, CDCl3) δ(ppm) : 8.19 (s, 1H) , 7.46 (d , 2H, *J* =8.4 Hz) , 7.19 (d , 2H, *J* =8.4 Hz), 4.20 (s, 2H), 2.35 (s, 3H) [28].

2-chloro-N-*m*-tolylacetamide (9): Yield 84%, yellow solid, 1HNMR (300MHz, CDCl3) δ(ppm): 8.20 (s,1H) , 7.40 (s ,1H) , 7.37 (d , 1H , *J* =8.1 Hz) , 7.28-7.24 (m, 1H), 7.02 (d , 1H , *J* =7.2Hz) , 4.20 (s ,2H), 2.38 (s ,3H) [29]

2-chloro-*N*-(3-chlorophenyl)acetamide (10): Yield 77%, colourless solid, 1HNMR (300MHz, CDCl3) δ(ppm): 8.27 (s, 1H), 7.70 (s, 1H), 7.44 (d, 1H, *J* = 6.9Hz), 7.34-7.28 (m, 1H), 7.19-7.17 (m, 1H), 4.21 (s, 2H). [28]

2-chloro-N-(4-bromophenyl)acetamide (11): Yield 65%, brown solid, 1HNMR (300MHz, CDCl3) δ(ppm) : 9.27 (s, 1H), 6.91-6.88 (m, 2H), 6.76 (d, 2H, *J* =8.4Hz), 3.48 (s, 2H). [28]

2-chloro-N-*o*-tolylacetamide (12): Yield 79%, White solid, 1HNMR (300MHz, CDCl3) δ(ppm): 8.26 (s, 1H), 7.90 (d, 1H, *J* =7.8Hz), 7.28-7.32 (m, 2H), 7.14 (d, 1H, *J* =7.2Hz), 4.28 (s, 2H), 3.32 (s, 3H). [29]

2-chloro-*N*-(naphthalene-1-yl)acetamide (13): Yield 76%, Brown solid, 1HNMR (300MHz, CDCl3) δ(ppm): 8.80 (s, 1H), 8.02 (d, 1H, *J* =7.5Hz), 7.93 (t, 2H, *J* =8.1Hz), 7.79 (d, 1H, *J* =8.1Hz), 7.63-7.54 (m, 3H), 4.37 (s, 2H). [30] (300MHz, CDCl3) δ(ppm): 7.87 (s, 1H), 7.19-711 (m, 3H), 4.28 (s, 2H), 2.26 (s, 6H) [31].

2-chloro-N-(3-chloro,4-fluorophenyl)acetamide (15): Yield 72%, White solid, 1HNMR (300MHz, CDCl3) δ(ppm): 8.24 (s, 1H), 7.77-7.74 (m, 1H), 7.43-7.37 (m, 1H), 7.28 (s, 1H), 4.21 (m, 2H)[31].

1-(4-benzylpiperazin-1-yl)-2-chloroethanone (16): Yield 55%, Colourless solid, 1HNMR (300MHz, CDCl3) δ(ppm): 7.28-7.15 (m, 2H), 7.09-6.99 (m, 3H), 4.01 (s, 2H), 3.99-3.85 (m, 4H), 3.83 (s, 2H), 3.65-3.59 (m, 4H) [32]

2-chloro-1-(4-(3-chlorophenyl)piperazin-1-yl)ethanone (17): Yield 42%, White solid,1HNMR (300MHz, CDCl3) δ(ppm): 7.19 (s, 1H), 7.15 (t, 1H, *J* =8.1Hz), 6.82 (d, 1H, *J*= 8.4Hz), 6.75 (d, 1H, *J* = 7.8Hz), 4.04 (s, 2H), 3.79-3.66 (m, 4H), 3.17-3.12 (m, 4H) [33]

1-(4-tert-butylpiperazin-1-yl)-2-chloroethanone (18): Yield 69%, White solid, 1HNMR (300MHz, CDCl3) δ (ppm): 4.02 (s, 2H), 3.52-3.43 (m, 4H), 3.39-3.30 (m, 4H), 1.40 (s, 9H) [34].

1-(4-(benzo[1,3]dioxol-5-ylmethyl)piperazine-1yl)-2-chloroethanone (19): Yield 52%, Off white solid, 1HNMR (300MHz, CDCl3) δ(ppm): 6.86 (s, 1H), 6.75 (s, 2H), 5.95 (s, 2H), 4.06 (s, 2H), 3.64 (s, 2H), 3.52 (s, 2H), 3.45 (s, 2H), 2.47-2.45 (m, 4H), ^{13}C NMR ($CDCl_3$) δppm: 164.94, 147.80, 109.83, 108.08, 107.60, 101.14, 61.49, 46.06, 45.36, 41.58; Anal. Calc. for.$C_{14}H_{17}ClN_2O_3$: C 56.66, H 5.77, N 9.44; found C 56.93, H 5.65, N 9.40.

2-chloro-1-1(4-phenylpiperazin-1-yl)ethanone (20): Yield 55%, Off white solid, 1HNMR (300MHz, CDCl3) δ(ppm): 7.95-7.82 (m, 2H), 7.43-7.33 (m, 2H), 6.98 (m, 1H), 4.02 (s, 2H), 3.95-3.82 (m, 4H), 3.35-3.24 (m, 4H) [35].

2-chloro-1-(4-(2,3-dichlorophenyl)piperazine-1-yl)ethanone (21): Yield 55%, Brown solid, 1HNMR (300MHz, CDCl3) δ(ppm): 7.28-7.13 (m, 2H), 6.95-6.93 (m, 1H), 4.12 (s,

2H), 3.82-3.81 (m, 2H), 3.72-3.71 (m, 2H), 3.10-3.03 (m, 4H); ^{13}C NMR ($CDCl_3$) δppm: 164.08, 144.77, 129.44, 123.00, 122.89, 120.62, 114.12, 46.70, 46.16, 41.85; Anal. Calc. for $C_{12}H_{13}Cl_3N_2O$; C 49.86, H 4.26, N 9.11, found C 49.66, H 4.06, N 9.21.

2-chloro-N-(4-hydroxypiperidin-1-yl)acetamide (22): Yield 55%, Dirty green Solid, 1HNMR (300MHz, CDCl3) δ(ppm): 5.24 (s, 1H), 5.14-5.11 (m, 1H), 4.11-4.01 (m, 4H), 3.83-3.72 (m, 2H), 2.01-1.77 (m, 4H)[36].

2-chloro-*N*-cyclohexylacetamide (23): Yield 82%, Colourless solid, 1HNMR (300MHz, CDCl3) δ(ppm): 6.45 (s, 1H), 4.04 (s, 2H), 3.86-3.75 (m, 1H), 1.96-1.92 (m, 2H), 1.78-1.62 (m, 4H), 1.47-1.34 (m, 2H), 1.28-1.15 (m, 2H) [30].

2-chloro-N-isopropylacetamide (24): Yield 75%, solid, 1HNMR (300MHz, CDCl3) δ(ppm): 6.41 (s, 1H) , 4.28-4.09 (m ,1H), 4.03 (s, 2H), 1.22 (s ,6H) [38]

2-chloro-N-cyclopropylacetamide (25): Yield 70%, Colourless Solid, 1HNMR (300MHz, CDCl3) δ(ppm) 12.07 (s, 1H), 3.61 (s, 2H), 1.87-1.65 (m, 1H), 1.45-1.40 (m, 4H) [39].

2-chloro-*N*-cyclopentylacetamide (26): Yield 78%, Colourless Solid, 1HNMR (300MHz, CDCl3) δ(ppm): 6.52 (s, 1H), 4.27-4.17 (m, 1H), 4.01 (s, 2H), 2.03-1.97 (m, 2H), 1.73-1.56 (m, 4H), 1.46-1.40 (m, 2H) [40].

N-butyl-2-chloroacetamide (27): Yield 74%, White solid, 1HNMR (300MHz, CDCl3) δ(ppm): 7.35 (s, 1H), 3.45-3.34 (m, 2H), 3.19 (s, 2H), 2.14-2.05 (m, 2H), 2.04-1.99 (m, 2H), 1.21-1.11 (m, 3H) [40].

[1]H Spectra of the new compounds

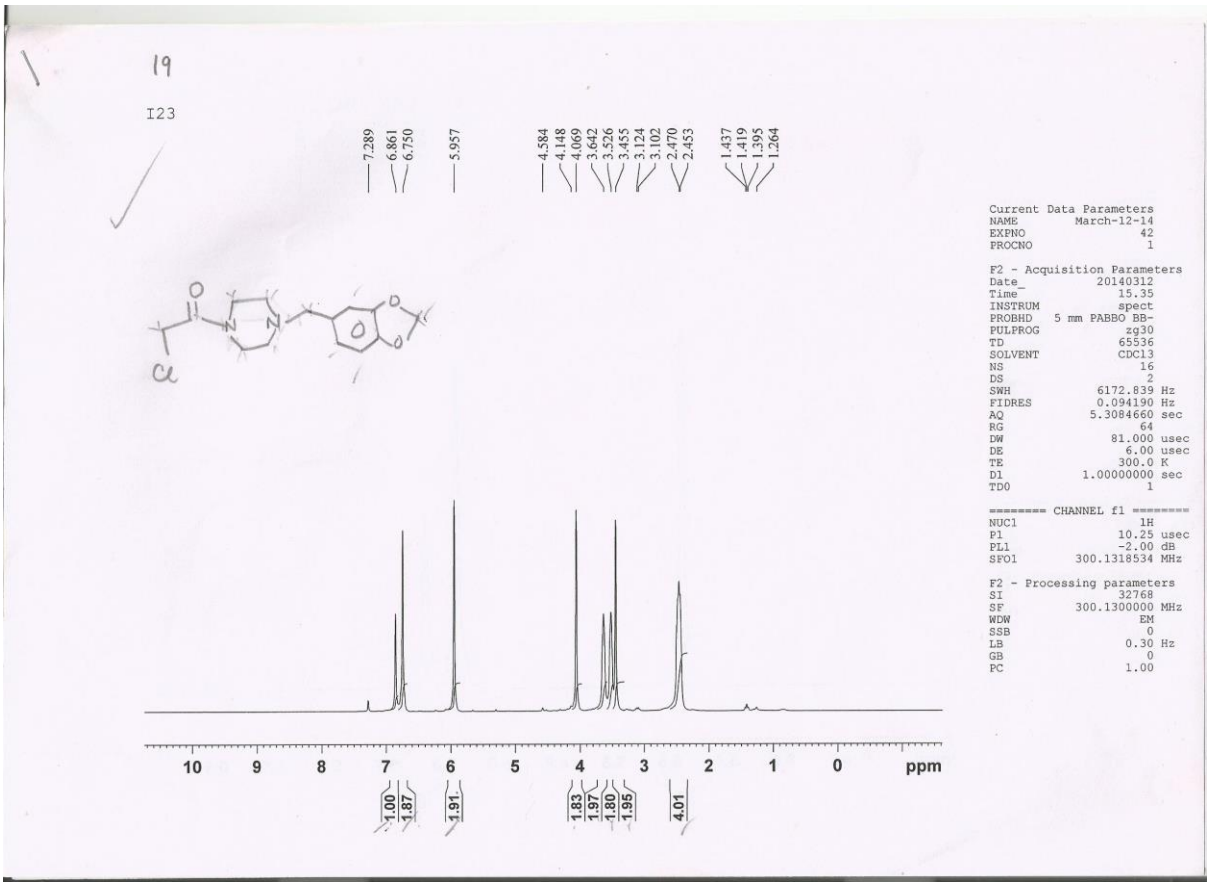

Figure1: [1]H Spectra of the compound 19

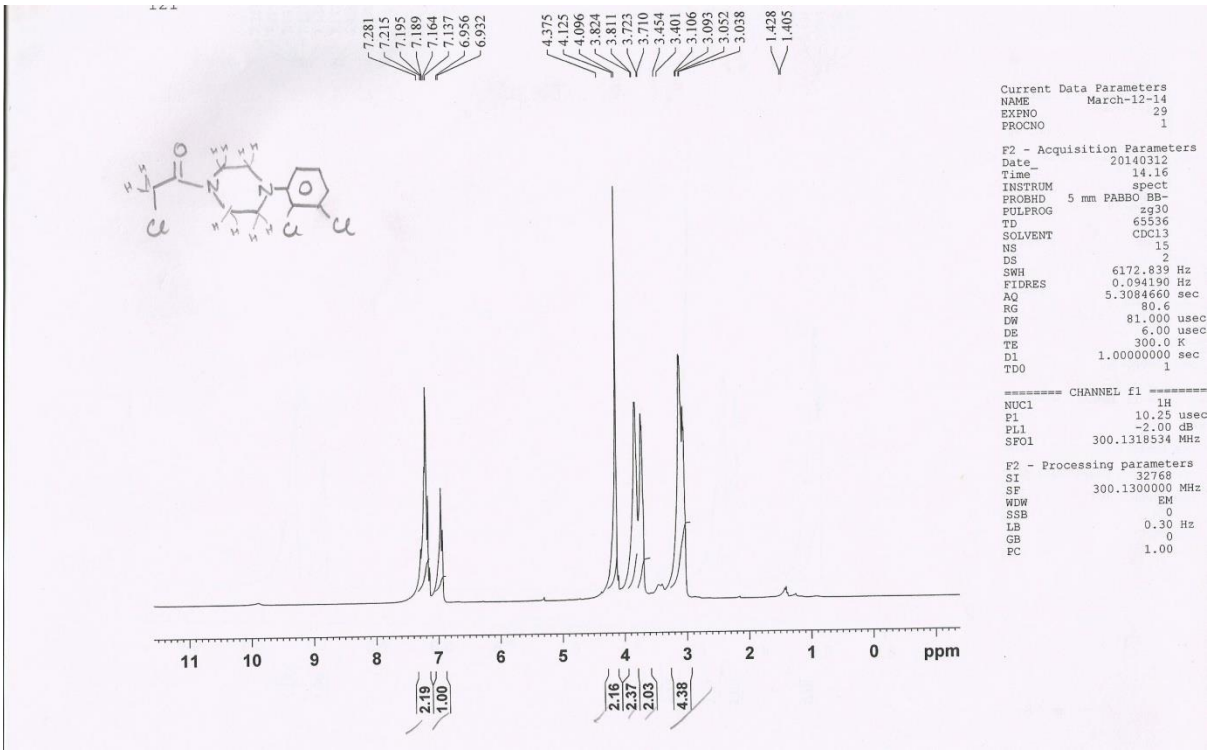

Figure2: ^{1}H Spectra of the compound 21

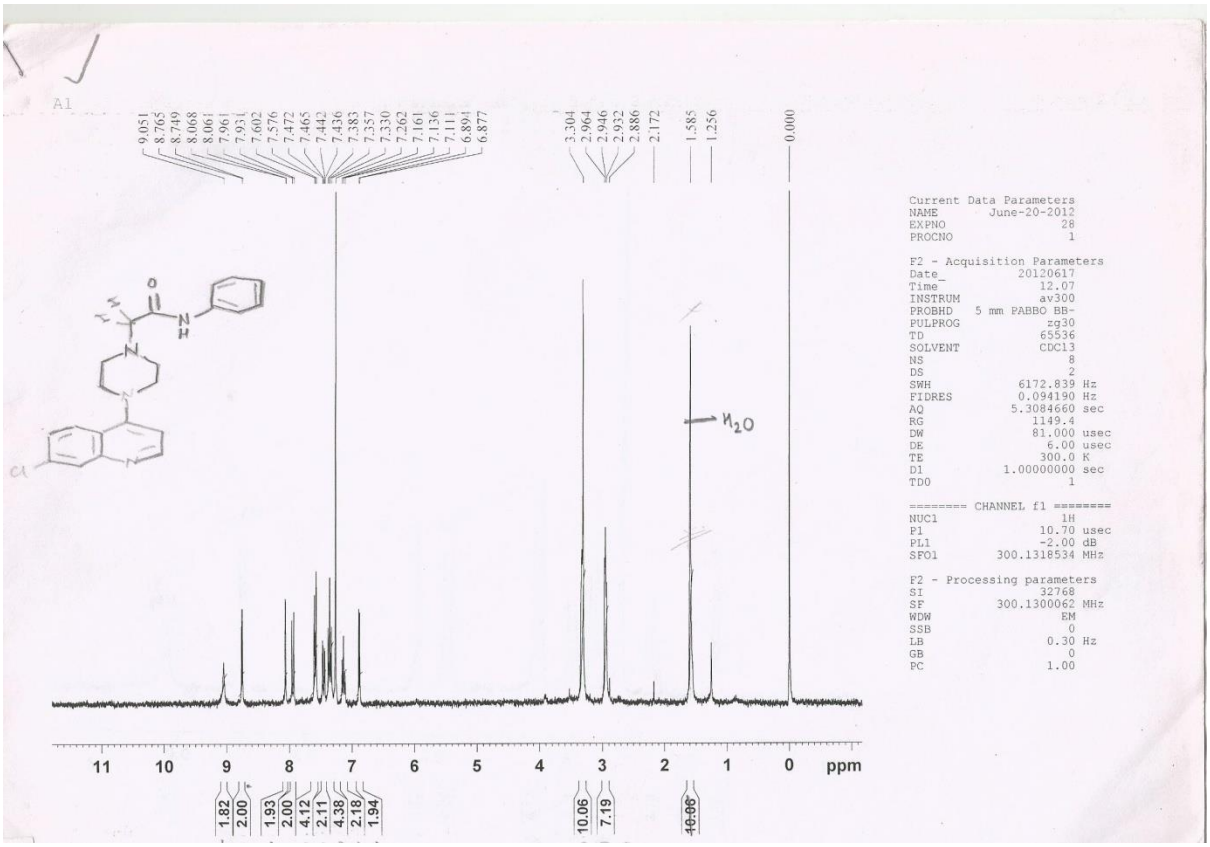

Figure3: ^{1}H Spectra of the compound A1

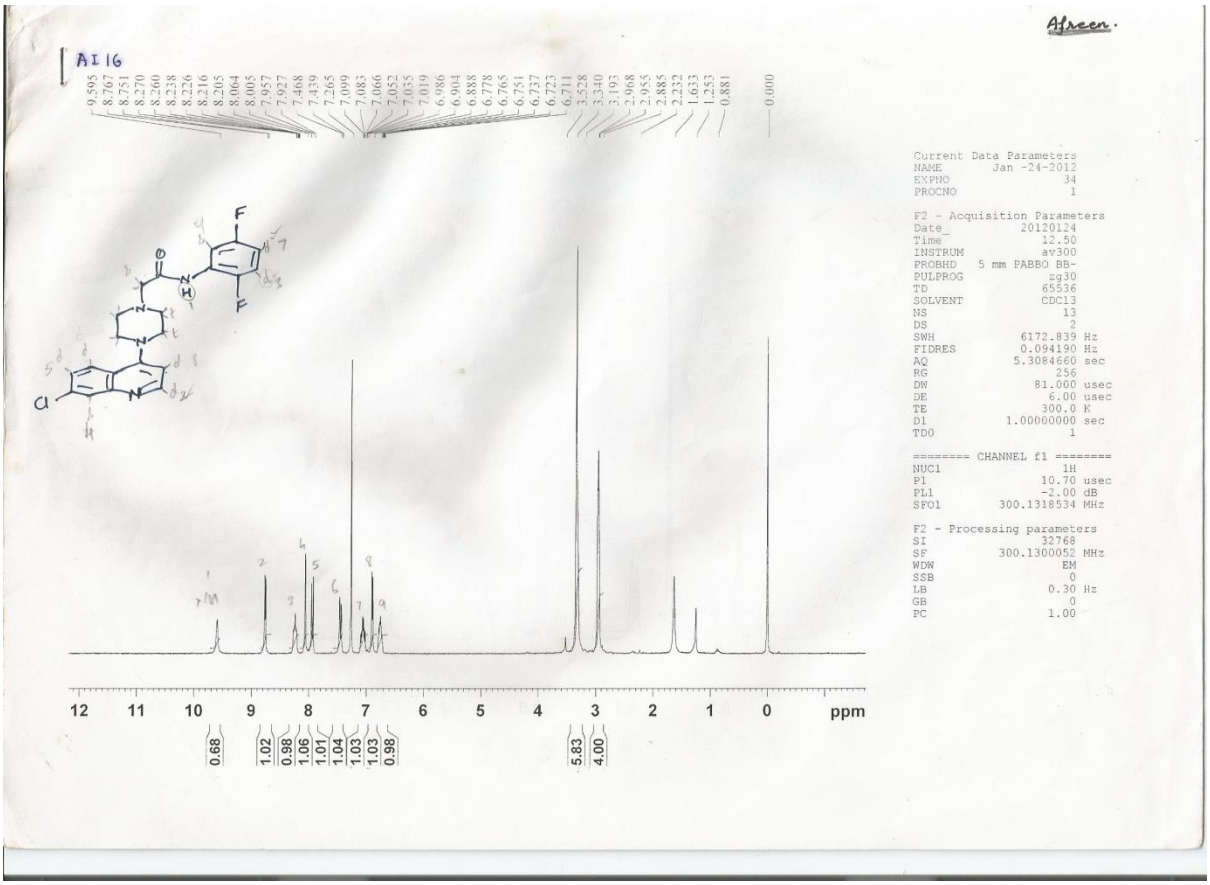

Figure4: ^{1}H Spectra of the compound A3

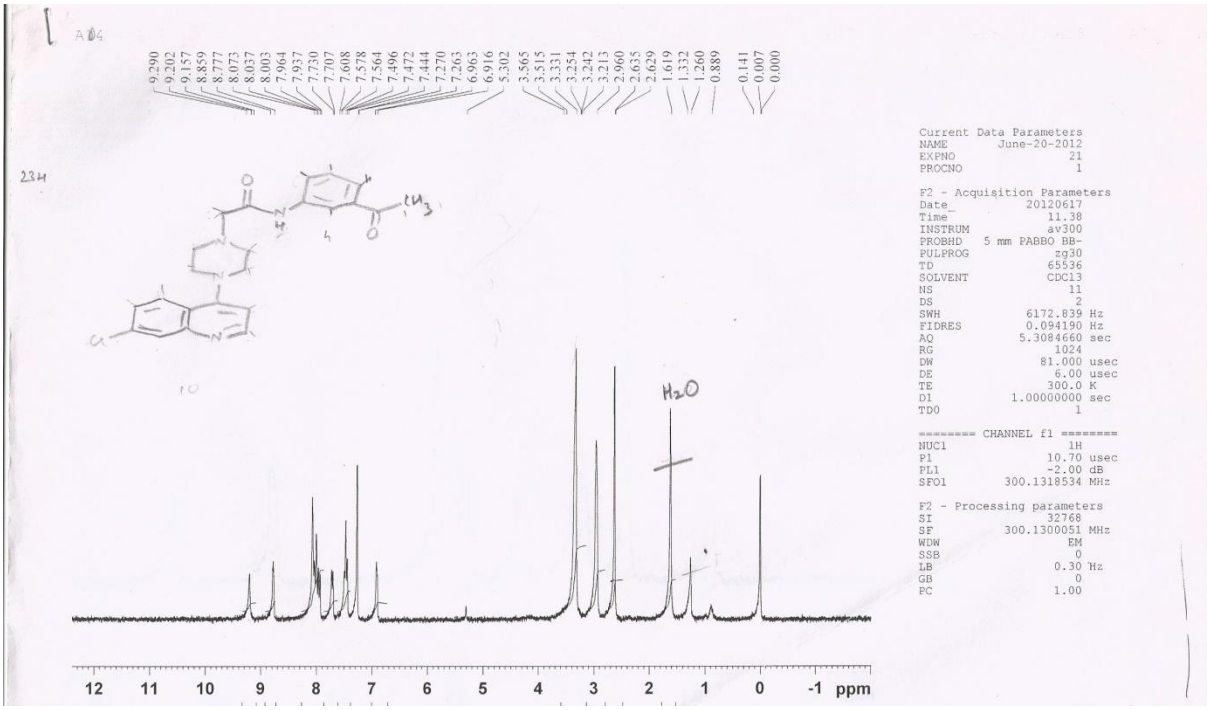

Figure5: ^{1}H Spectra of the compound A4

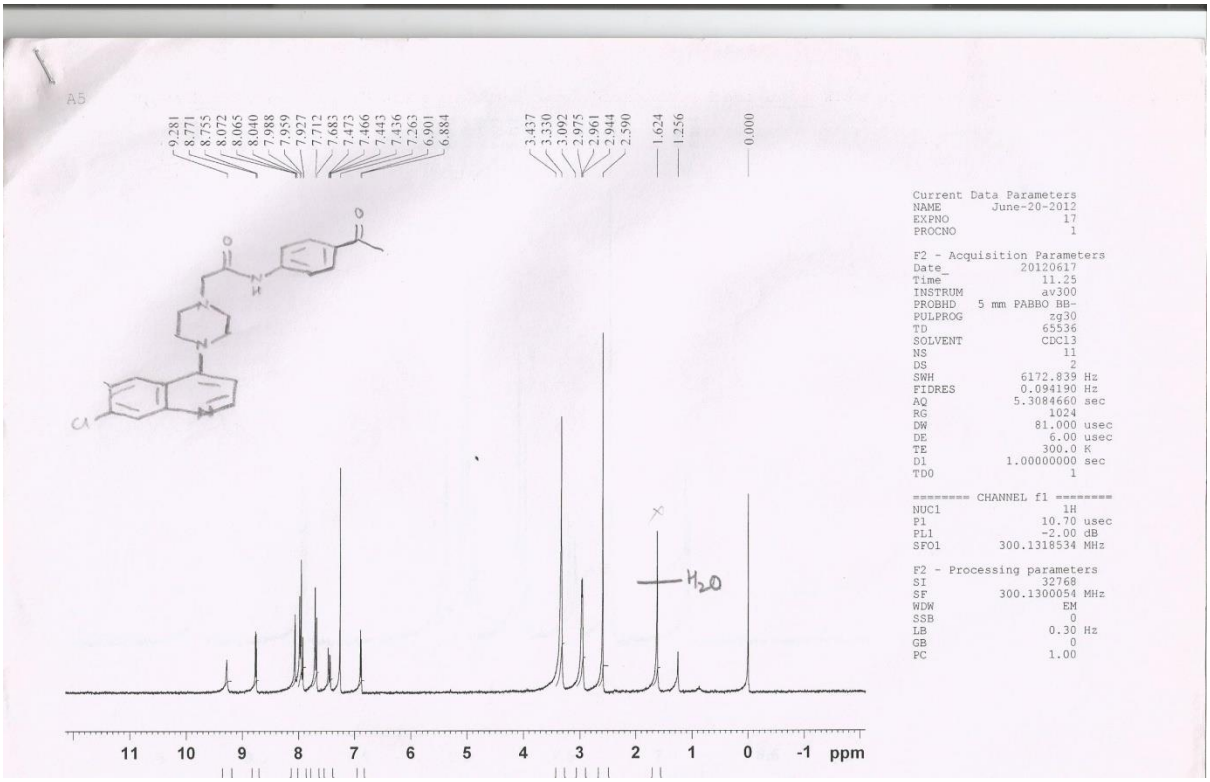

Figure6: ^{1}H Spectra of the compound A5

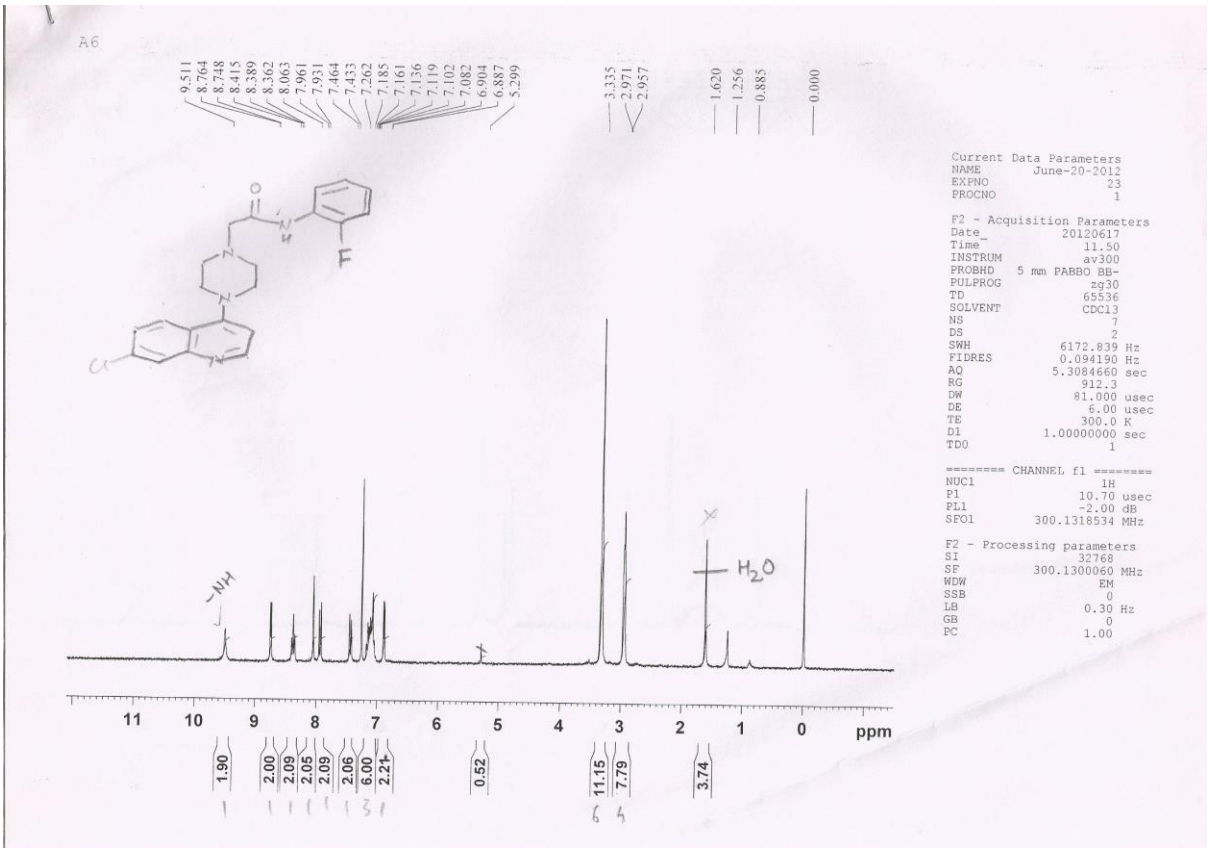

Figure7: ^{1}H Spectra of the compound A6

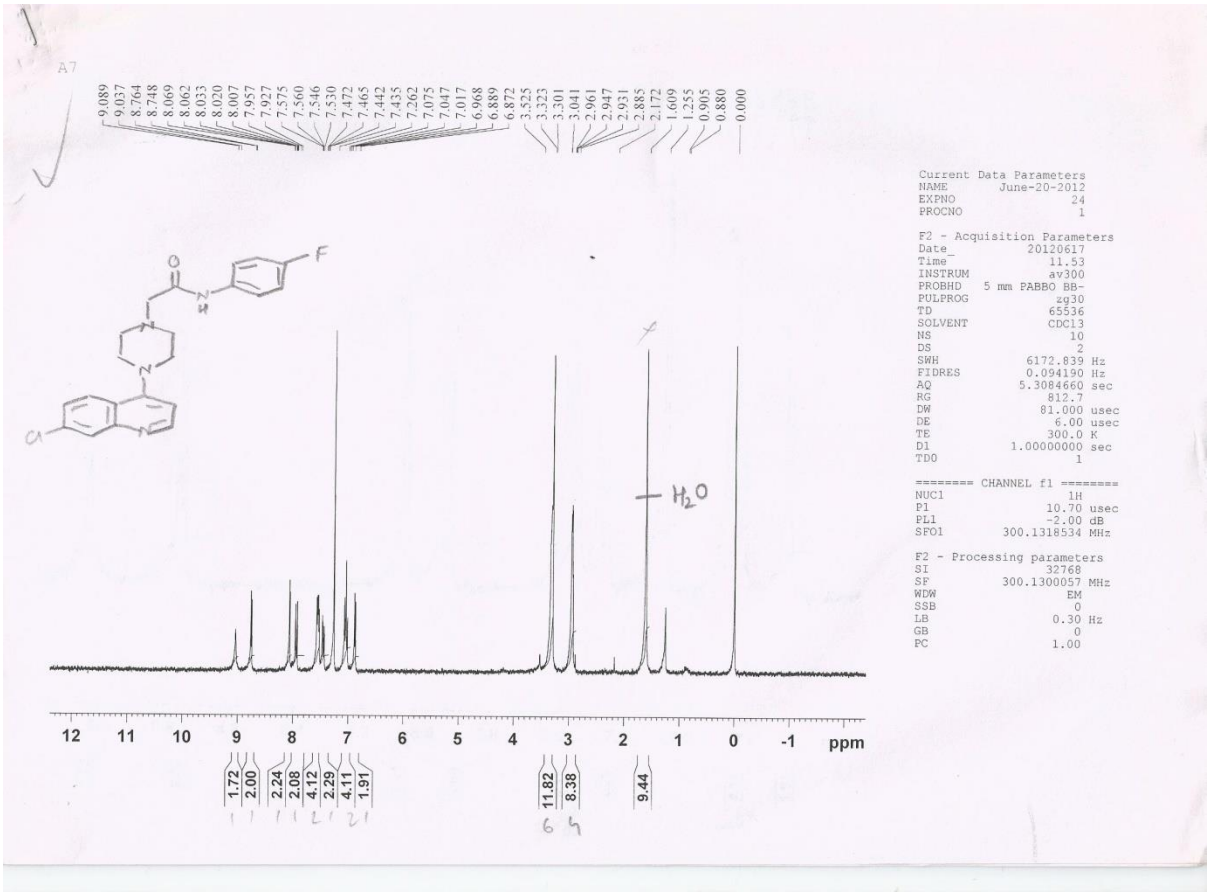

Figure8: ^{1}H Spectra of the compound A7

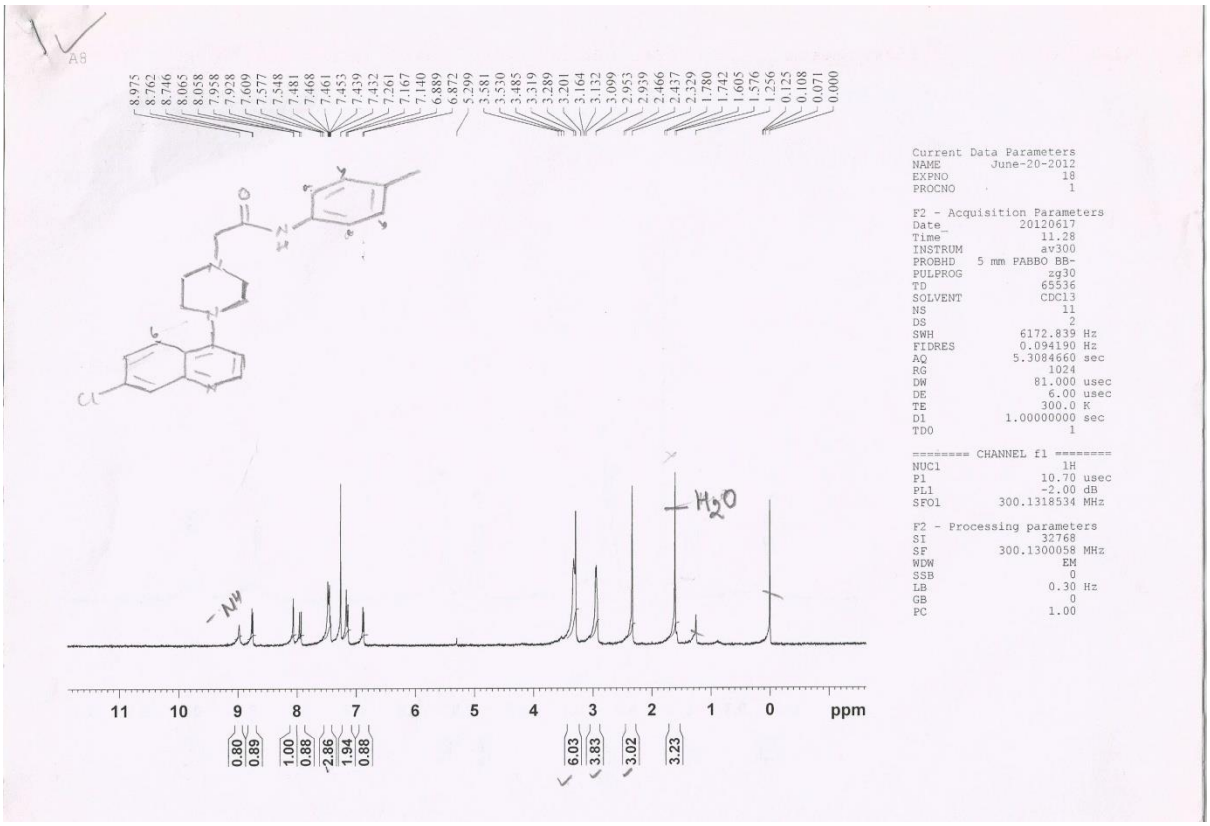

Figure9: ^{1}H Spectra of the compound A8

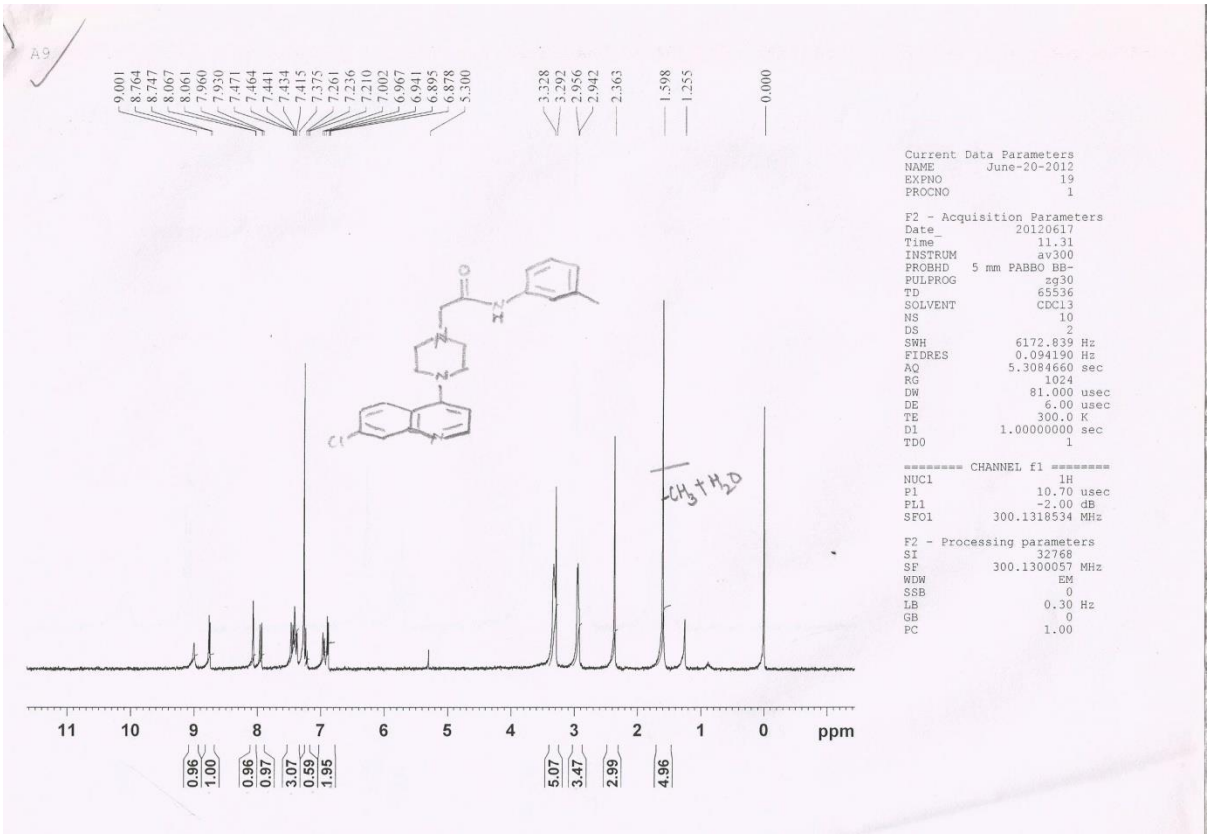

Figure10: ^{1}H Spectra of the compound A9

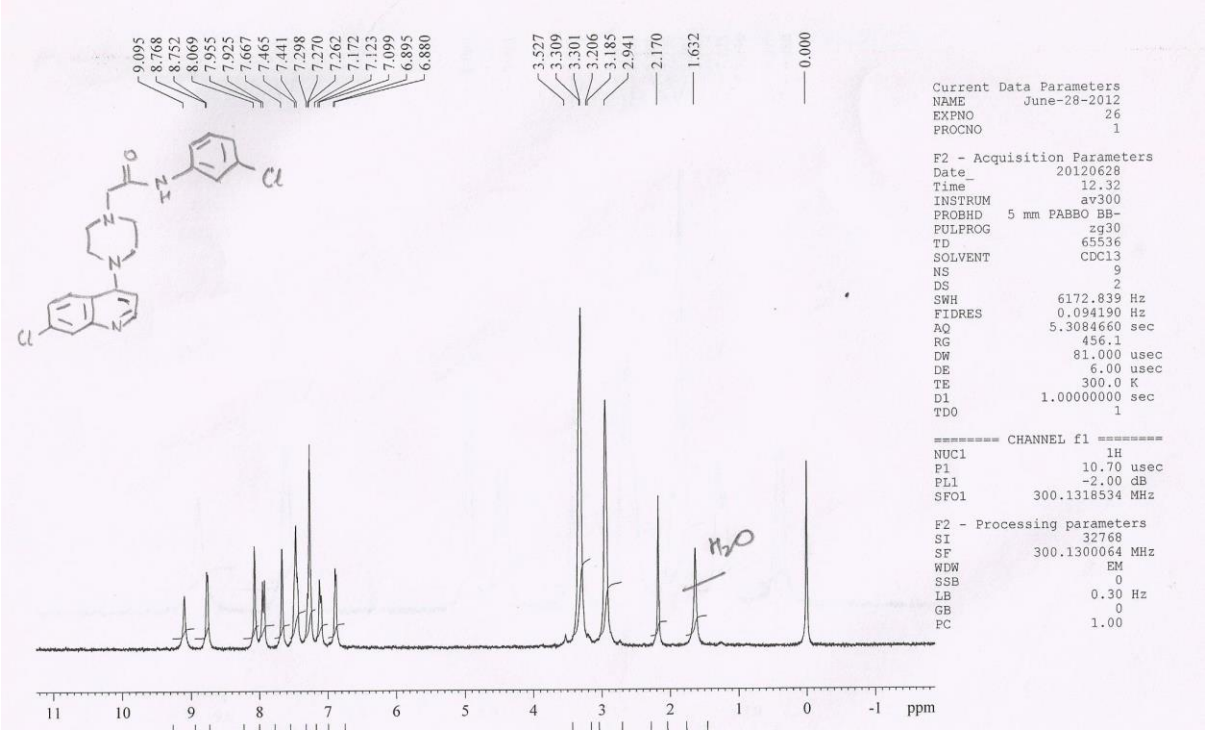

Figure11: ^{1}H Spectra of the compound A10

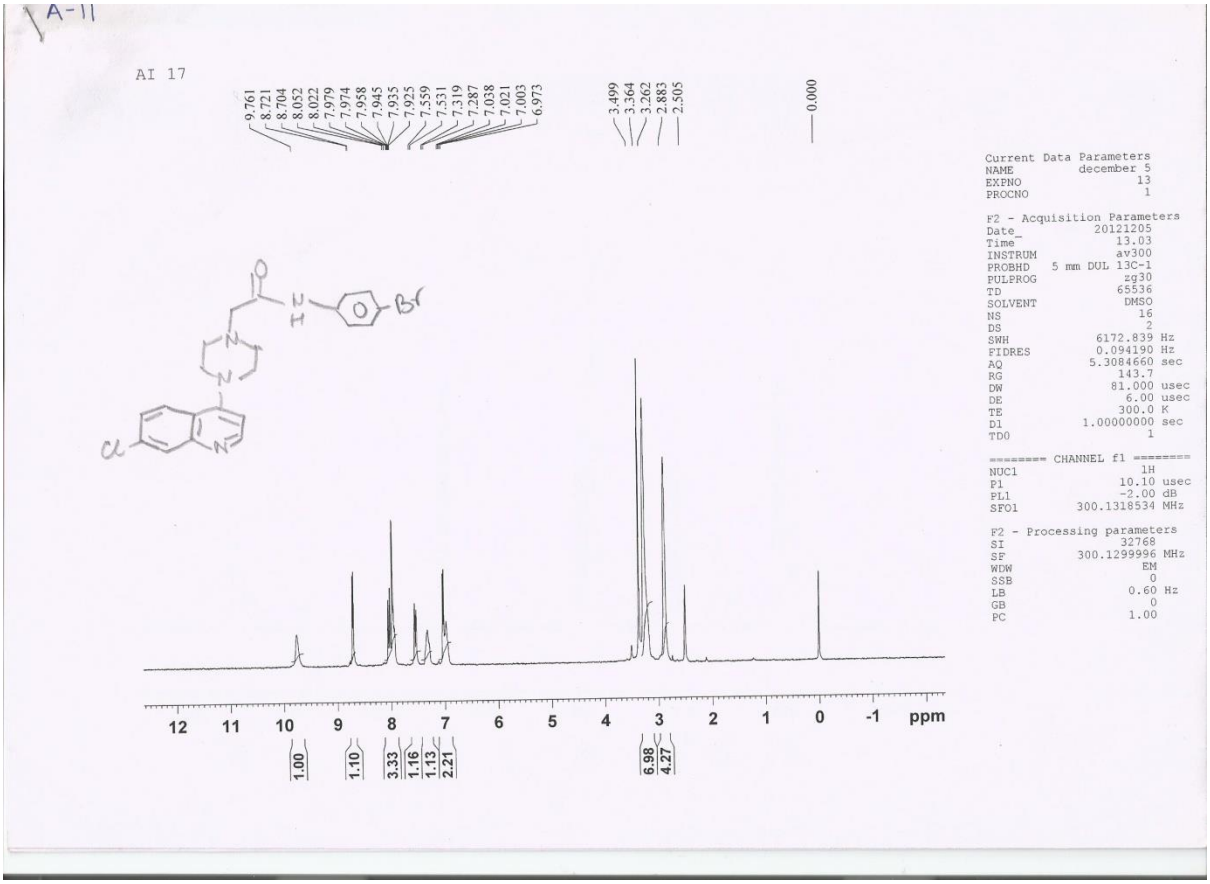

Figure12: ^{1}H Spectra of the compound A11

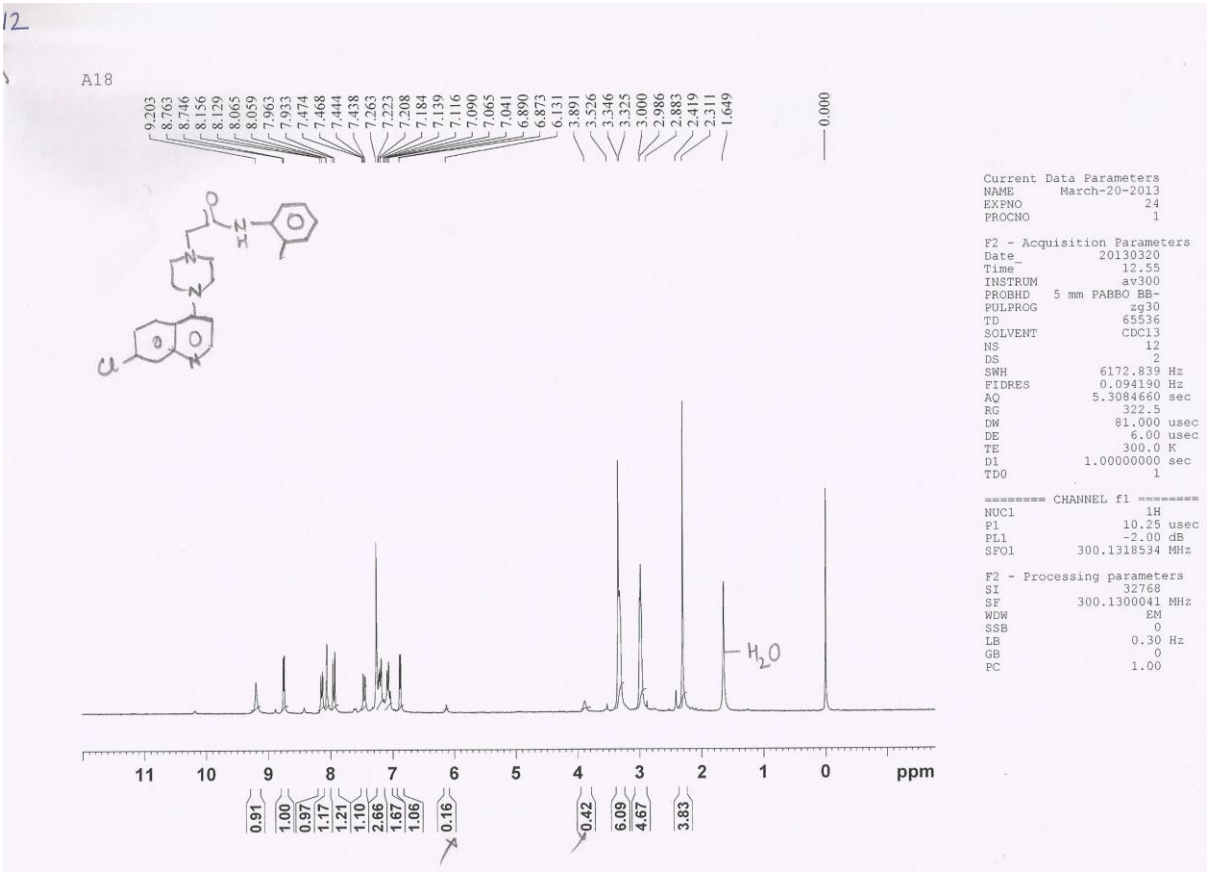

Figure13: ^{1}H Spectra of the compound A12

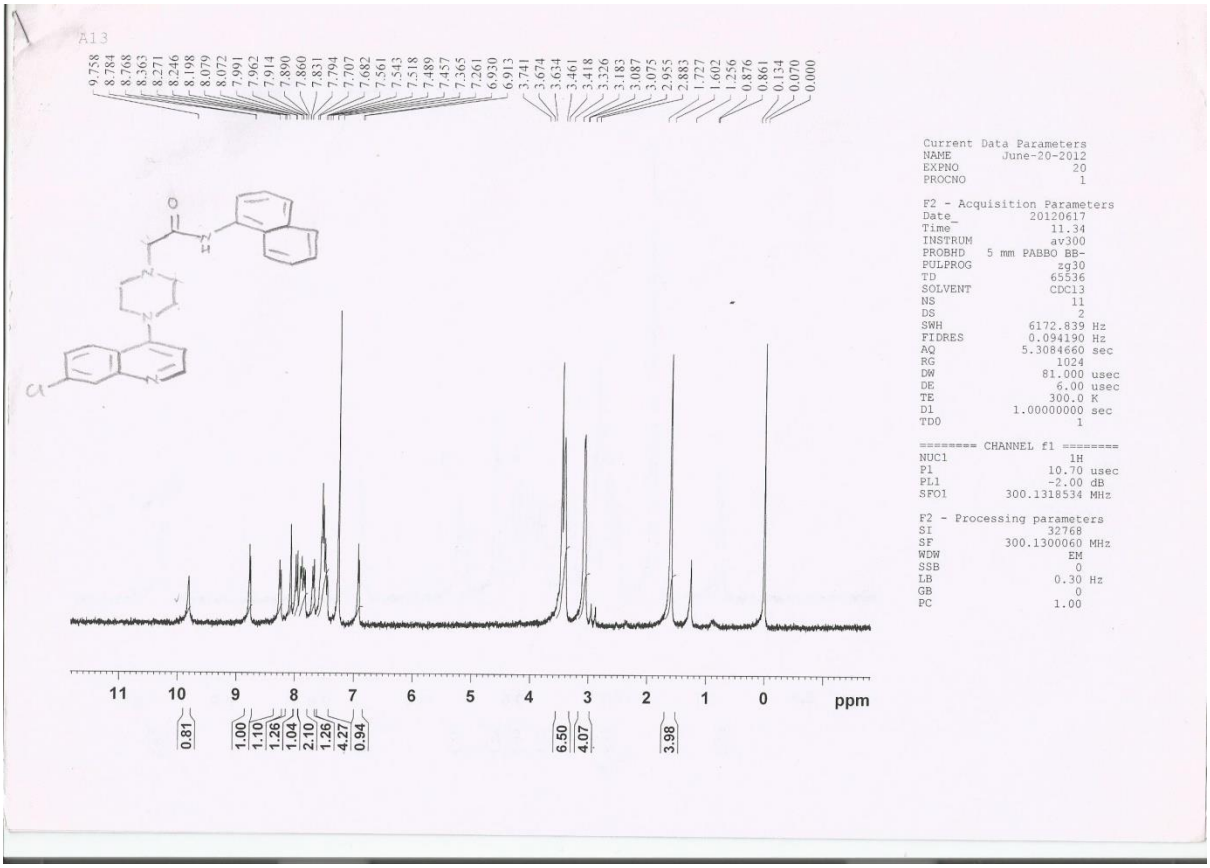

Figure14: ^{1}H Spectra of the compound A13

Figure15: ^{1}H Spectra of the compound A14

Figure16: ^{1}H Spectra of the compound A15

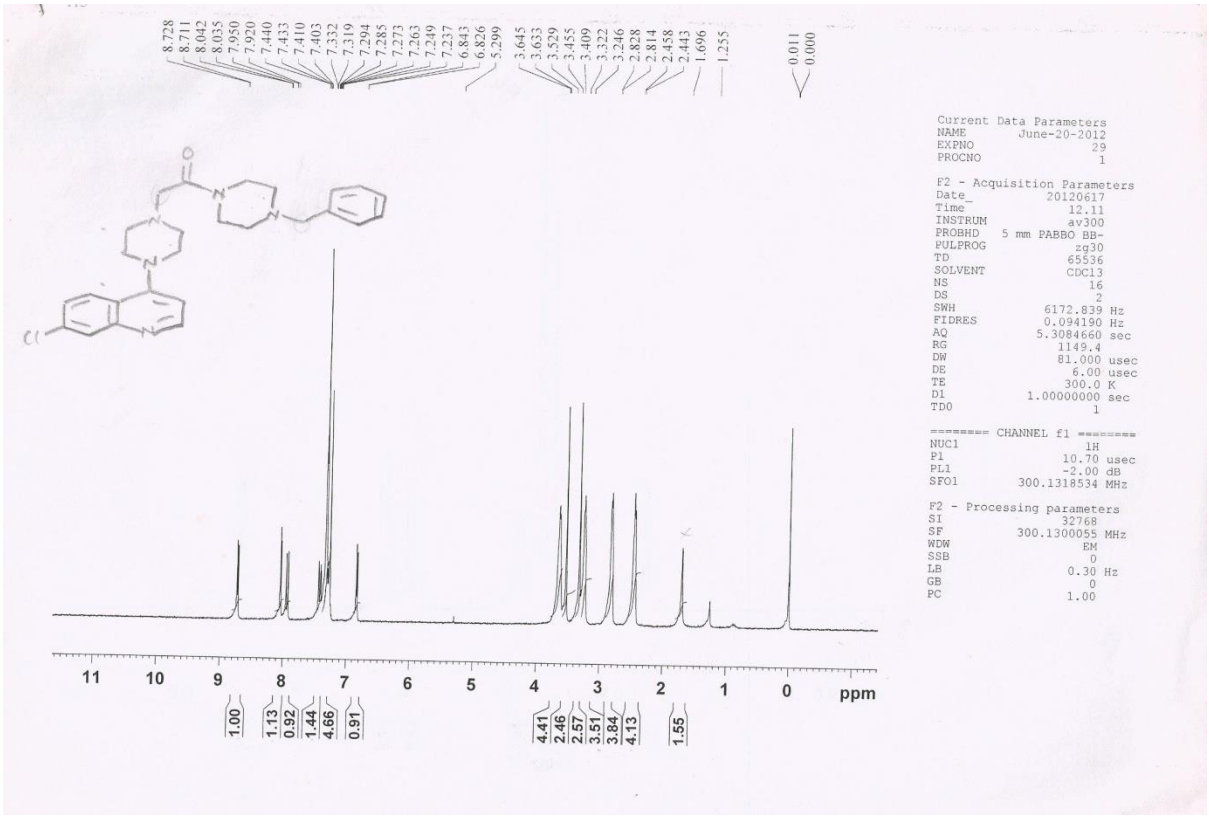

Figure17: ^{1}H Spectra of the compound A16

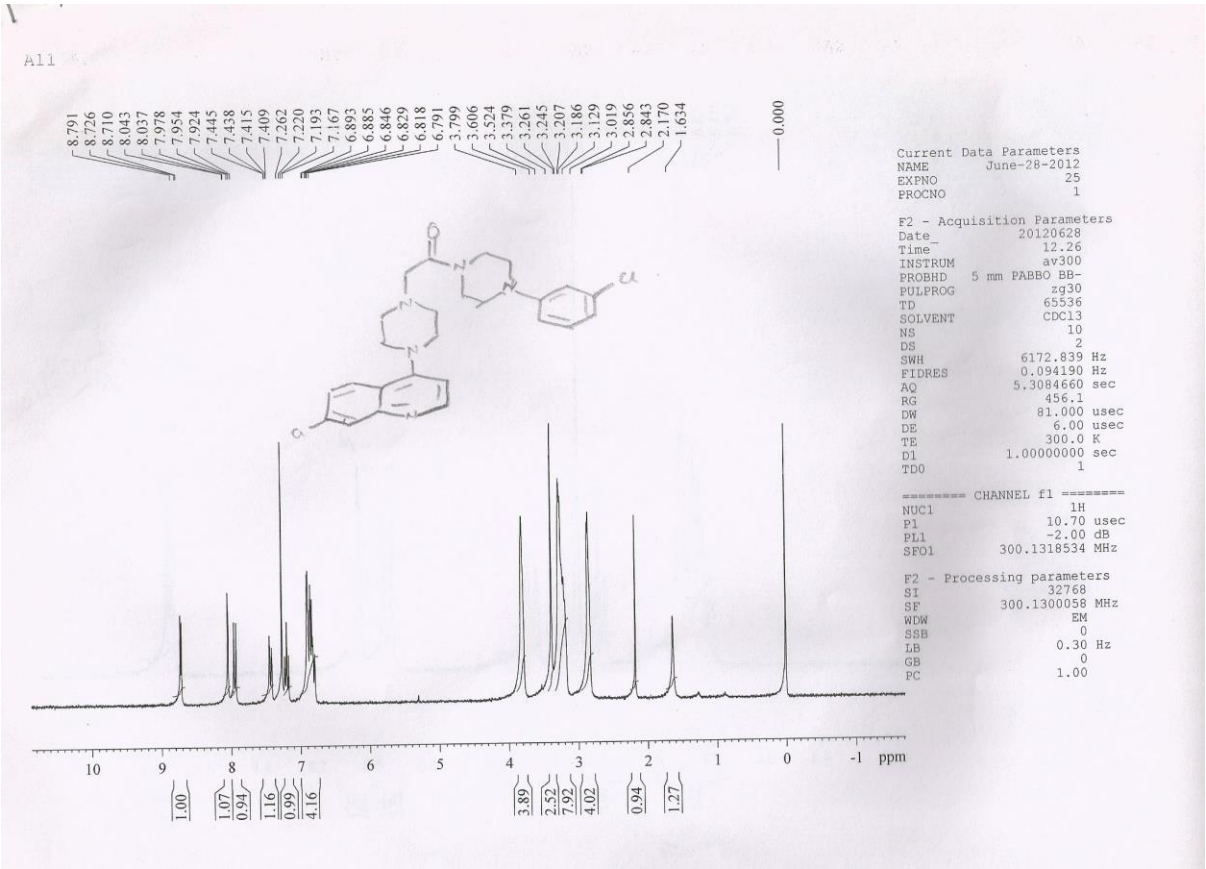

Figure18: ^{1}H Spectra of the compound A17

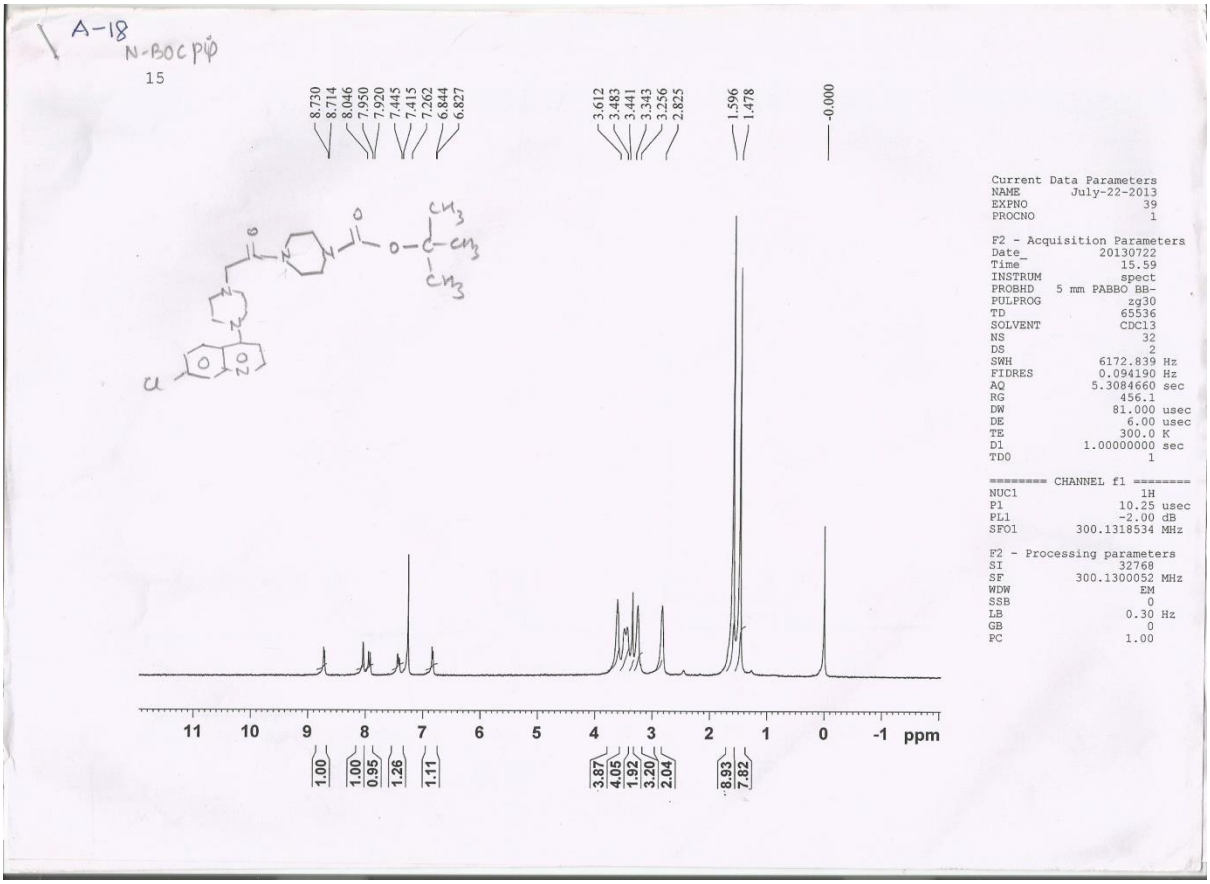

Figure19: ^{1}H Spectra of the compound A18

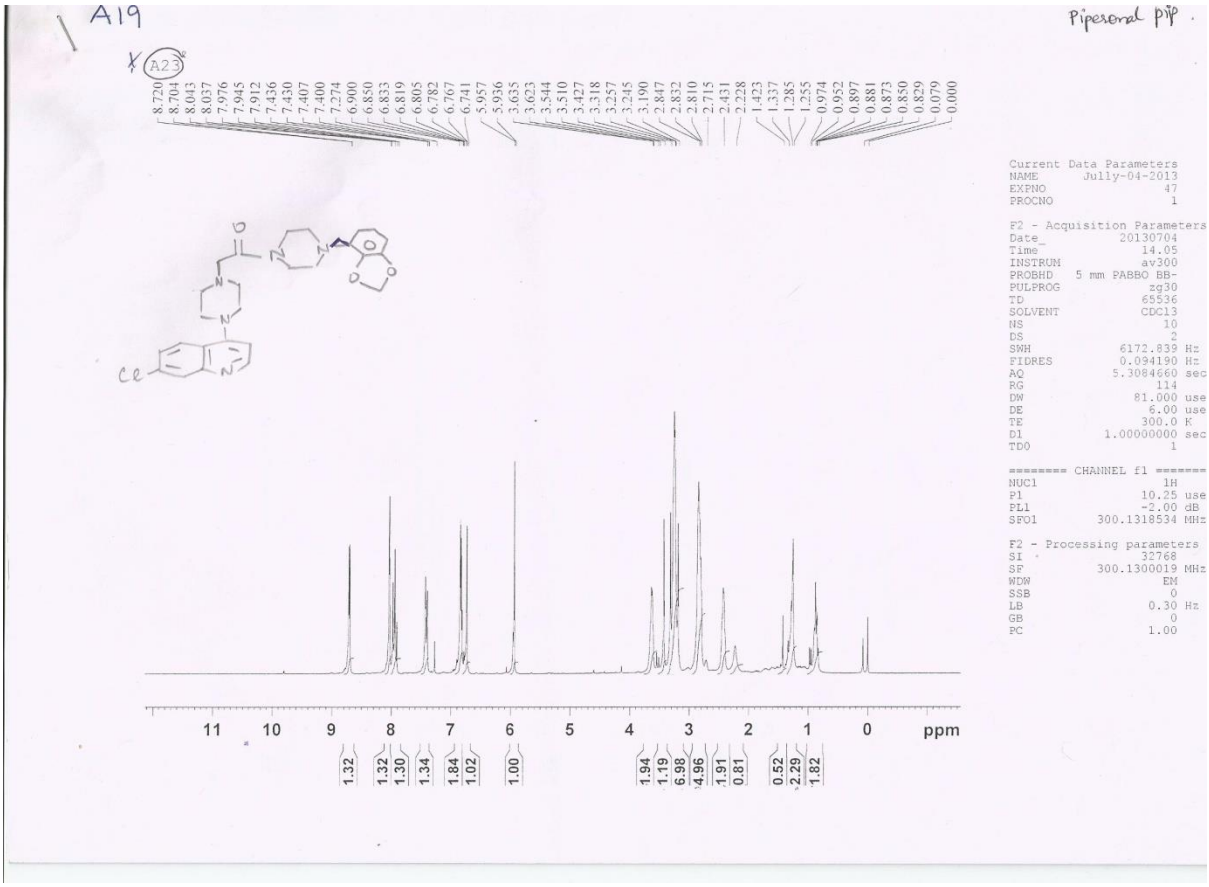

Figure20: ^{1}H Spectra of the compound A19

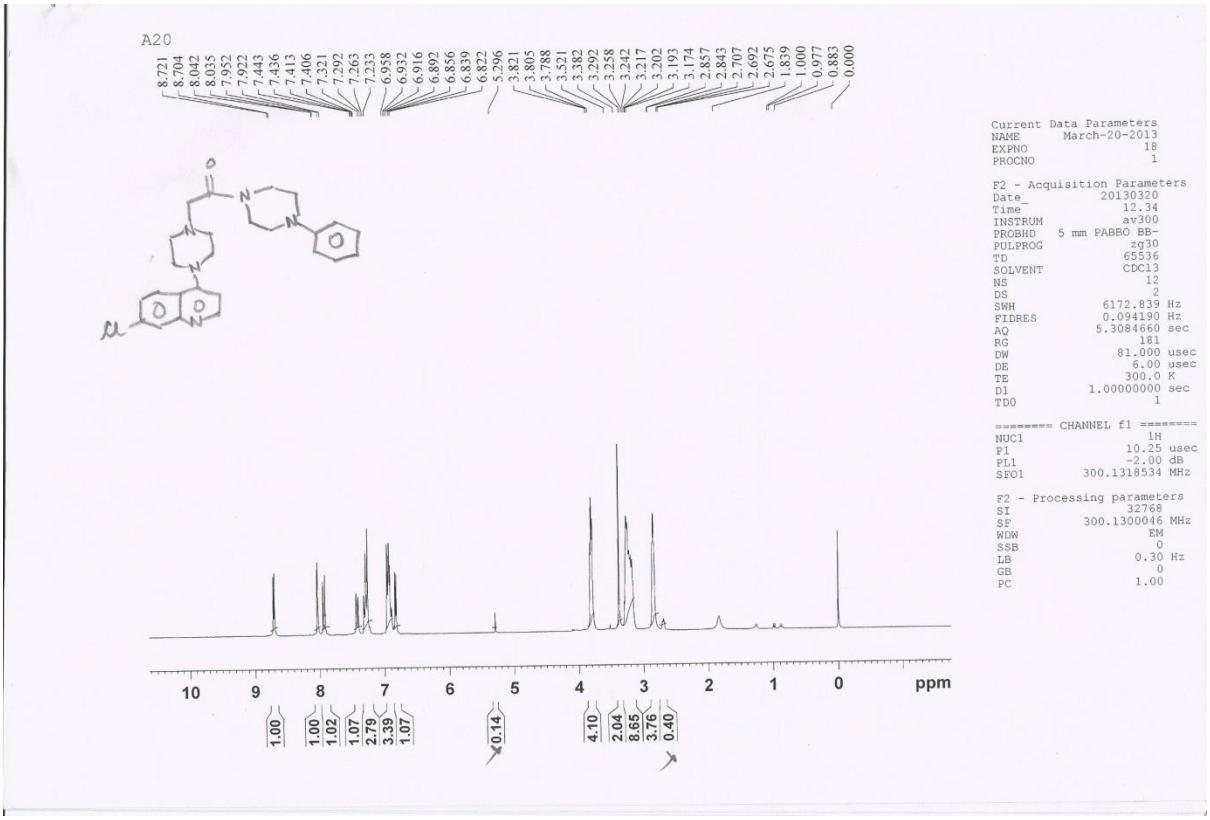

Figure21: ^{1}H Spectra of the compound A20

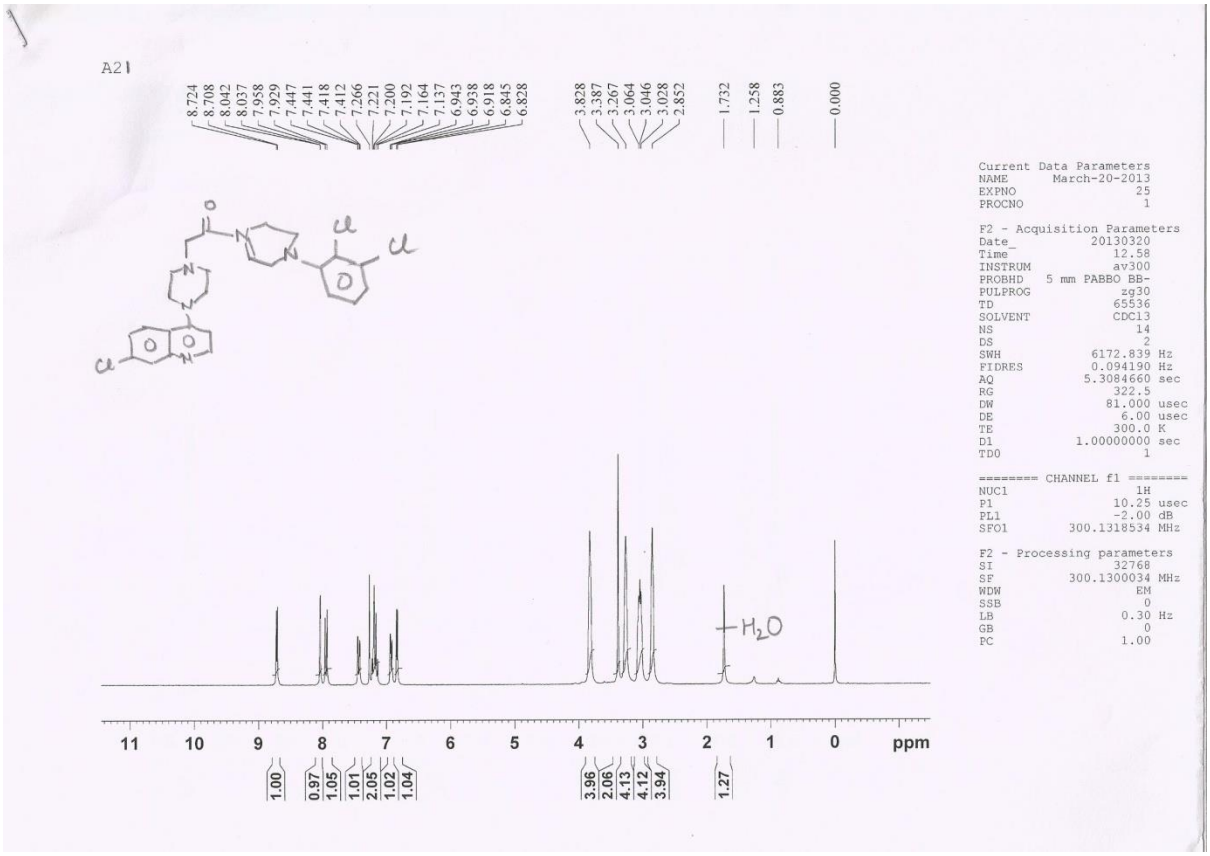

Figure22: ^{1}H Spectra of the compound A21

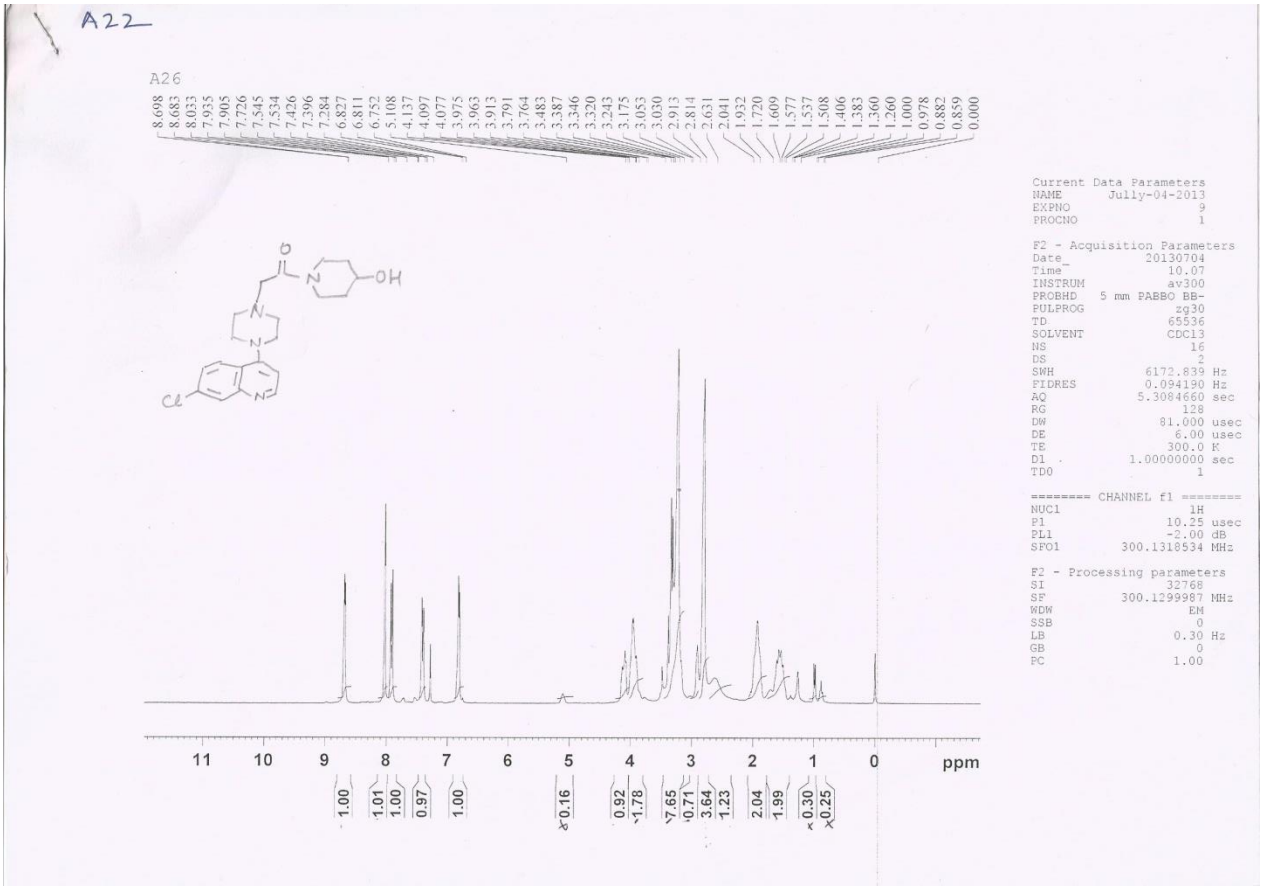

Figure23: ^{1}H Spectra of the compound A22

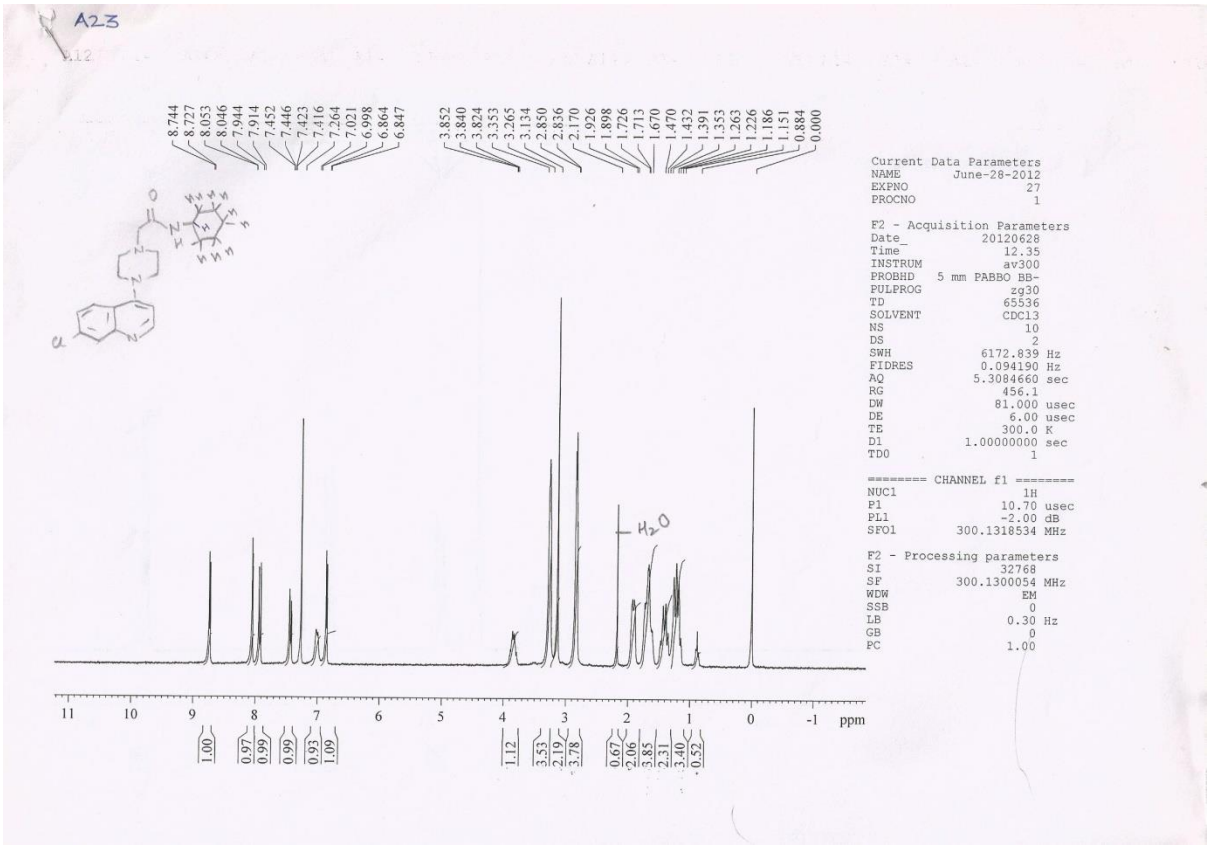

Figure24: ^{1}H Spectra of the compound A23

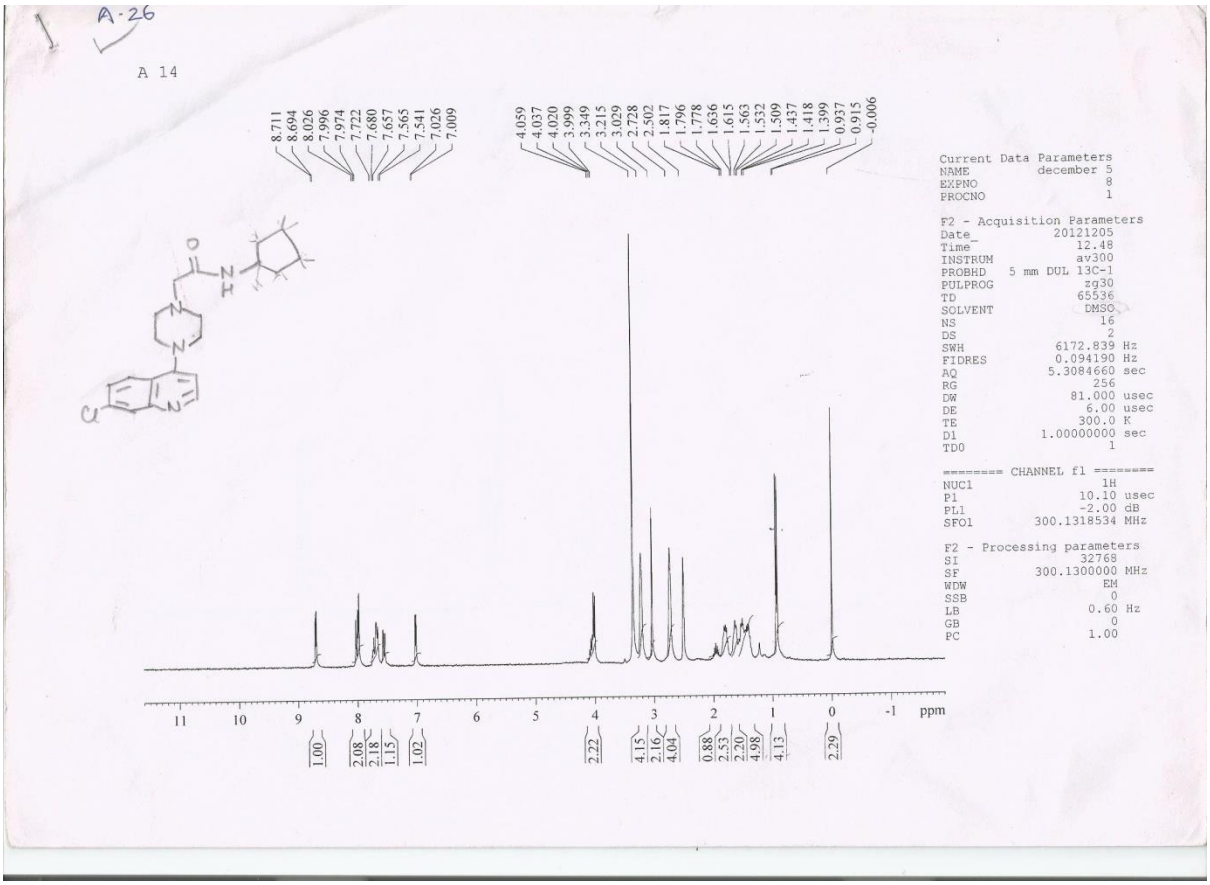

Figure25: ^{1}H Spectra of the compound A26

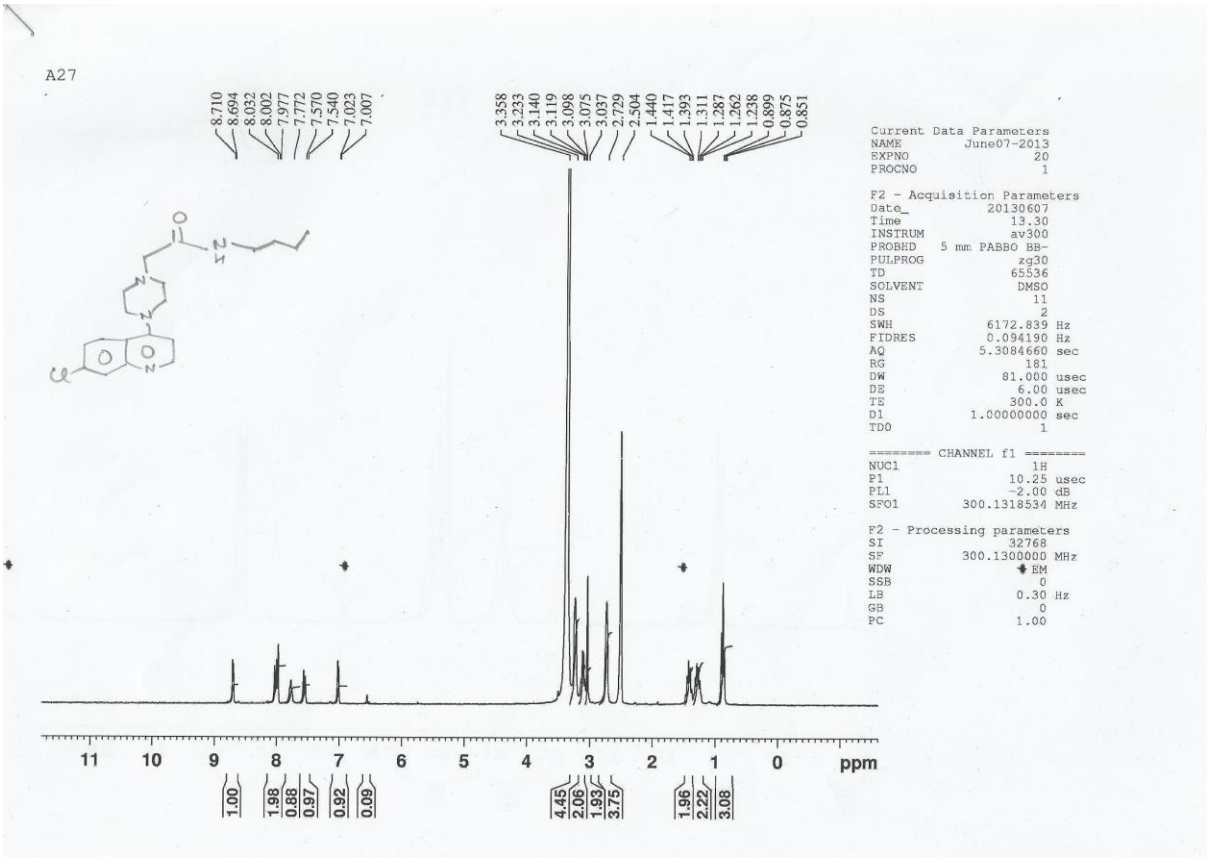

Figure26: ^{1}H Spectra of the compound A27

References:

[24] Z. Xiaohe, Q. Yu, Y. H,S. Xiuqing and Z. Rugang, Chem Biol Drug Des 2010; 76, 330-339

[25] J. Qinggang , D. Yang , X. Wang , C. Chen, Q. Deng , G. Zhiqiang , L. Yuan a , Xiaolan Yang, F. Liao; Bioorg. Med. Chem. 2014, 22, 3405–3413

[26] Gonzalez-Rosende, M. E.; Olivar, T.; Castillo, E.; Sepulveda-Arques, J. *Arch. Pharm.* 2008, *341*, 690-695.

[27] H. Behbehani, and H. M.Ibrahim, *Molecules* 2012, *17*, 6362-6385

[28] R. Kumar, M. Kaur , M. S. Bahia, Om Silakari, Eur. J. Med. Chem. 2014, 80, 83-91.

[29] T. R. K. Reddy , C. Li, X. Guo, P. M. Fischer, L. V. Dekker, Bioorg. Med. Chem. 2014, 22, 5378–5391

[30] Jain NP , Upasani CD , Kalkotwar RS and Jain UN, Research Journal of Pharmaceutical, Biological and Chemical Sciences, 2013, 3, 1470-1480.

[31] Chen Hong , Wen Luo, , Dong Yao, Ya-Bin Su, Xin Zhang, Run-Guo Tian, Chao-Jie Wang Bioorg. Med. Chem. 2014, 22 3213–3219

[32] Mingming Zhang, Weiliang Zhu, Yingxia Li, Eur. J. Med. Chem. 2013, 62, 301-310.

[33] Cunlong Zhang , Chunyan Tan , Xuyu Zu , Xin Zhai , Feng Liu , Bizhu Chu, Xiaohua Ma, Yuzong Chen, Ping Gong, Yuyang Jiang , Eur. J. Med. Chem. , 2011, 46, 1404-1414

[34] Colabufo, Nicola Antonio; Berardi, Francesco; Perrone, Roberto; Rapposelli, Simona; Digiacomo, Maria; Vanni, Michael; Balsamo, Aldo, J Med Chem. 2008, 51, 7602-13.

[35] Stephen J. Shuttleworth, Daniel Nasturica, Christian Gervais, M. Arshad Siddiqui, Robert F. Rando and Nola Lee, Bioorg Med. Chem. Lett., 2000, 10, 2501-2504.

[36] Brown, Dennis A.; Kharkar, Prashant S.; Parrington, Ingrid; Reith, Maarten E. A.; Dutta, Aloke K., J. Med. Chem. 2008, 51, 7806–7819

[37] Pablo Wessig and Kristian Möllnitz, J. Org. Chem. 2008, 73, 4452–4457.

[38] Wu, Chun-Fang; Zhao, Xin; Lan, Wen-Xian; Cao, Chunyang; Liu, Jin-Tao; Jiang, Xi-Kui; Li, Zhan-Ting, J. Org. Chem. 2012, 77, 4261−4270.

[39] Musso, David L.; Cochran, Felicia R.; Kelley, James L.; McLean, Ed W.; Selph, Jeffrey L.; Rigdon, Greg C.; Orr, G. Faye; Davis, Ronda G.; Cooper, Barrett R.; Styles, Virgil L.; Thompson, James B.; Hall, William R., J. Med. Chem., 2003, 46, 3-6.

[40] Christian Jö st, Christoph Nitsche, Therese Scholz, Lionel Roux, and Christian D. Kle J. Med. Chem. 2014, 57, 7590−7599