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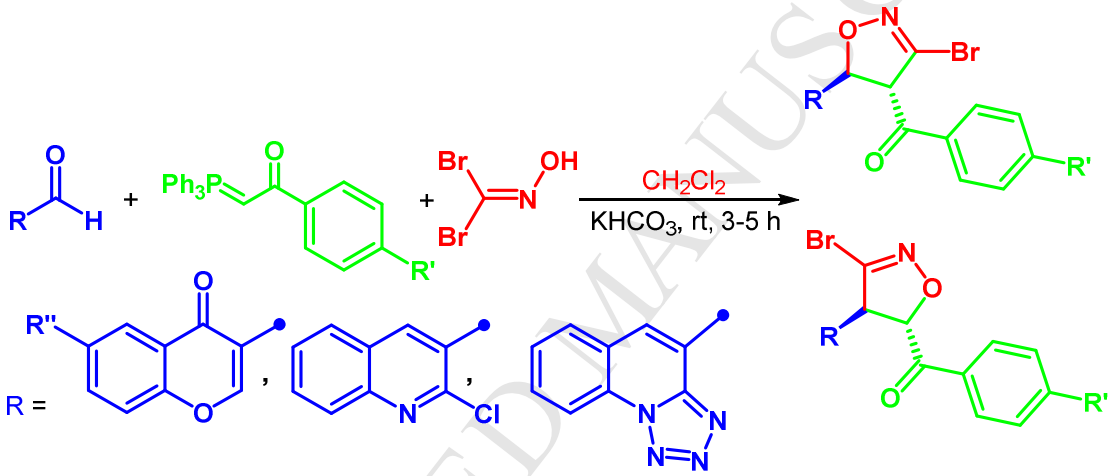

Efficient One Pot and Chemoselective Synthesis of Functionalized 3-Bromo-4,5-dihydroisoxazole Derivatives *via* 1,3-Dipolar Cycloaddition Reactions of Nitrile Oxides

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Abstract— A novel, metal-free and chemoselective approach for the synthesis of 4,5-dihydroisoxazole derivatives has been developed by the reaction of readily accessible starting materials including 4-oxo-4*H*-chromene-3-carbaldehyde, 1-phenyl-2-(1,1,1-triphenyl-λ^5-phosphanylidene)ethan-1-one and dibromoformaldoxime under mild conditions in the presence of $KHCO_3$.

Keywords: 4-Oxo-4*H*-chromene-3-carbaldehyde, 1-Phenyl-2-(1,1,1-triphenyl-λ^5-phosphanylidene)ethan-1-one, Dibromoformaldoxime, 4,5-Dihydroisoxazole, Chemoselective, One pot, Multicomponent Reactions
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1. Introduction

Heterocyclic compounds play a substantial role in pharmaceutical sciences and synthetic organic chemistry. They occur in many biologically active compounds and synthetic drugs, and they are also useful as key intermediates for synthesizing natural products.[1] They widely exist in additives and modifiers used in chemical industries such as cosmetics, plastics, reprographic and information storage.[1c] Among the most widely used nitrogen- and oxygen-containing five membered heterocycles are the 4,5-dihydroisoxazoles which are widespread in nature.

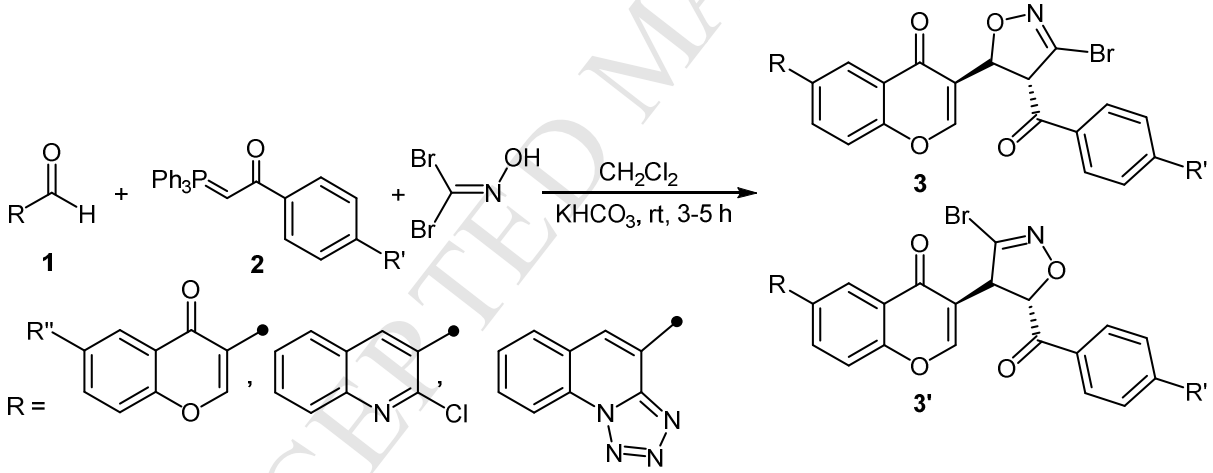
The 4,5-dihydroisoxazole (2-isoxazoline) moieties are important building blocks of numerous compounds with broad biological activities,[2] and are versatile intermediates for the synthesis of a variety of natural products. Also, they can be exposed to chemical transformations and converted into diverse useful compounds such as *β*-hydroxy carbonyls,[3] *α*,*β*-unsaturated oximes,[4] *γ*-amino alcohols,[5] and *β*-hydroxy nitriles.[6] Moreover, 2-isoxazoline units are important pharmacophores and exhibit significant biological activities such as antifungal,[7,8] anti-inflammatory,[9] antibacterial,[10] analgesic,[11] antiviral and anti-HIV.[12]

Isoxazoline derivatives also present an acceptable influence on animal models of thrombosis.[13] Some heterocyclic systems containing 2-isoxazoline such as isocarboxazid, oxacillin, valdecoxib, micafungin, and leflunomide are used as drugs.[14]

On the other hand, the quinoline scaffolds possess a wide spectrum of biological activities including anticancer, antiviral, anti-inflammatory,[15a] anticonvulsant,[15b] antimalarial[15c,15d] and non-opioid analgesics.[15e] Various approaches have been reported in the literature for the synthesis of functionalized 2-isoxazolines. One of the reliable strategies for the preparation of 4,5-dihydroisoxazoles is the 1,3-dipolar cycloaddition[16] of an alkene with nitrile oxide. In fact, in these reactions, the nitrile oxide has been achieved through *in situ* formation and then the [3+2] cycloaddition reaction has occured. In this context, we used bromonitrile oxide as the dipole body to form 3-bromo-4,5-dihydroisoxazole derivatives.

2. Results and Discussion

Recently, we have reported an efficient method for the synthesis of pyrazoles from 4-oxo-4*H*-chromene-3-carbaldehyde, hydroxylamine hydrochloride and hydrazonoyl chlorides by exploring a three-component 1,3-dipolar cycloaddition reaction in one-pot protocol.[17] As part of our continued interest in the synthesis of diverse heterocyclic compounds of biological significance,[18] we report herein the synthesis of some novel 3-bromo-4,5-dihydroisoxazole derivatives from simple dibromoformaldoxime, different aldehydes (4-oxo-4*H*-chromene-3-carbaldehyde, 2-chloroquinolone-3-carbaldehyde and tetrazolo[1,5-*a*]quinoline-4-carbaldehyde) and 1-phenyl-2-(1,1,1-triphenyl-λ^5-phosphanylidene)ethan-1-one and potassium hydrogen carbonate as base *via* a 1,3-dipolar cycloaddition three component reaction using dichloromethane as solvent at room temperature (Scheme 1).



Scheme 1. Synthesis of substituted 3-bromo-4,5-dihydroisoxazoles **3** and **3'**

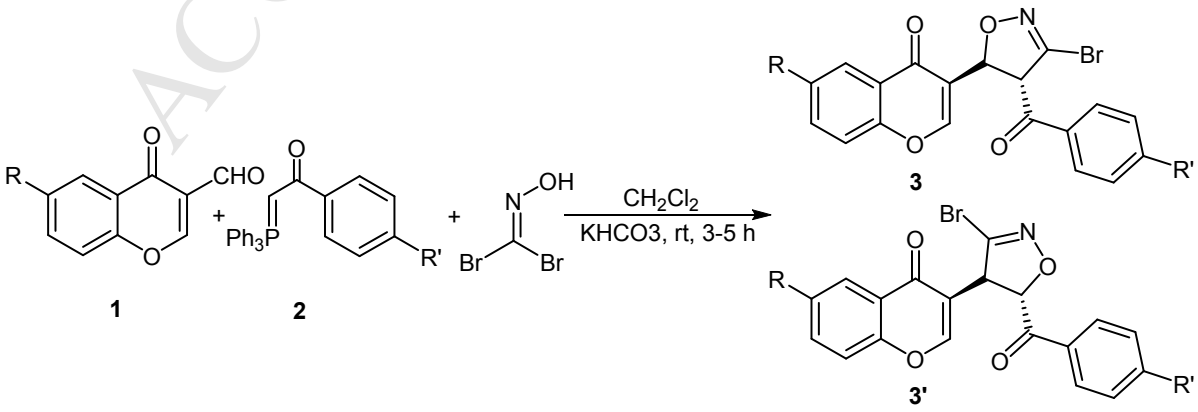
Quinolines and their derivatives are valuable component of pharmaceutically active compounds. The quinolone moiety can also be easily identified in the structure of various naturally occurring alkaloids. They have been accompanied by a wide spectrum of biological activities.[19,20] The fusion of quinoline scaffold to the tetrazole unit is noticed to grow the biological activity. The

tetrazole group is regarded as analogues to carboxylic group as a pharmacore and possesses wide range of pronounced activities such as anti-inflammatory,[21] anti-AIDS,[22] CNS dispersant,[23] anticonvulsant,[24] antimycobacterial,[25] etc.. In particular, tetrazolo[1,5-*a*]quinoline-4-carbaldehyde performs as a pivotal synthetic intermediate for the synthesis of new pharmaceutically valuable compounds[26]. Chromone and its derivatives exhibit a wide spectrum of medicinal properties including antimicrobial[27], antitumour,[28] and antiviral[29] activities. Therefore, given the biological properties of these three combinations and their availability, we decided to use these compounds to synthesize 4,5-dihydro isoxazole derivatives.

The synthesis of the title compounds involves the reaction of the aldehyde moiety with a Wittig reagent to form the *α*,*β*-unsaturated compound, which on 1,3-dipolar cyclization reaction with bromoformaldoxime in the presence of $KHCO_3$ base furnishes 3-bromo-4,5-dihydroisoxazoles in excellent yields. The progress of the reaction was monitored by TLC. After completion of the reaction, products **3** and **3'** as two diastereomers were obtained in 80-90 % yield. Additional functionalizations were investigated, as shown in Table 1 and Table 2. Various functional groups were introduced at the 4- and 5-position of 2-isoxazoline in excellent yields (80-90%).

As anticipated from our initial results, these reactions proceeded very cleanly at room temperature and no undesirable side reactions were observed.

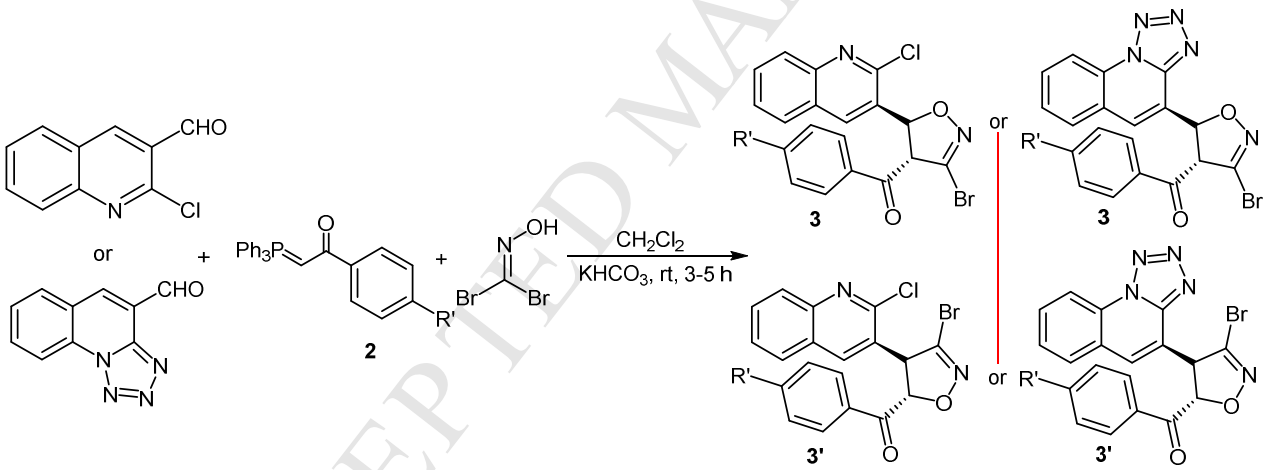
Table 1 Synthesis of 3-(4-benzoyl-3-bromo-4,5-dihydroisoxazol-5-yl)-4*H*-chromen-4-one derivatives



Entry	R	R’	Products	[a]Ratio of **3** : **3'**	Yield (%)
1	H	H	**3a**, **3'a**	86 : 14	90
2	H	Br	**3b**, **3'b**	94 : 6	85
3	H	Cl	**3c**, **3'c**	> 98 : 2	85
4	H	Me	**3d**, **3'd**	96 : 4	87
5	Cl	H	**3e**, **3'e**	> 98 : 2	82

[a]Measured by ^{1}H NMR spectroscopy

Table 2 Synthesis of [3-bromo-5-(2-chloroquinolin-3-yl)-4,5-dihydroisoxazol-4-yl](phenyl)methanone and (3-bromo-5-tetrazolo[1,5-*a*]quinolin-4-yl-4,5-dihydroisoxazol-4-yl)(phenyl)methanone derivatives



Entry	Aldehyde	R’	Products	[a]Ratio of **3** : **3'**	Yield (%)
1	2-chloroquinolone-3-carbaldehyde	H	**3f**, **3'f**	32 : 68	85
2	2-chloroquinolone-3-carbaldehyde	Br	**3g**, **3'g**	72 : 28	82
3	tetrazolo[1,5-*a*]quinoline-4-carbaldehyde	H	**3h**, **3'h**	76 : 24	80
4	tetrazolo[1,5-*a*]quinoline-4-carbaldehyde	Me	**3i**, **3'i**	> 98 : 2a	82

[a]Measured by ^{1}H NMR spectroscopy

The structure of all the products were confirmed upon careful analysis of the data obtained from IR, mass, ^{1}H NMR, and ^{13}C NMR spectra. The mass spectrum of **3a** displayed the molecular ion peak at the appropriate *m/z* value. In the IR spectrum of **3a**, two absorption bands at 1680 and 1632 cm^{-1}, two absorption bands at 1590 and 1464 cm^{-1}, and an absorption band at 1220 cm^{-1}, which are related to C=O, Ar and C-O stretching frequencies, clearly indicated the most significant functional groups of the product. The ^{1}H NMR spectrum of **3a** exhibited two signals at 5.42 and 6.04 ppm, readily recognized as two CH hydrogen atoms of the isoxazoline ring. A signal at 8.12 ppm belonged to the olefinic hydrogen. Seven other signals in the range of 7.43-8.17 ppm belong to the nine aromatic hydrogens gave rise to characteristic signals in the aromatic region of the spectrum. Observation of 17 distinct signals in the ^{1}H-decoupled ^{13}C NMR spectrum of **3a** is in agreement with the proposed structure. Finally the structure of the major regioisomer (**3'f**) of **3f** was confiremed by X-ray crystal structure analysis (Fig. 1).

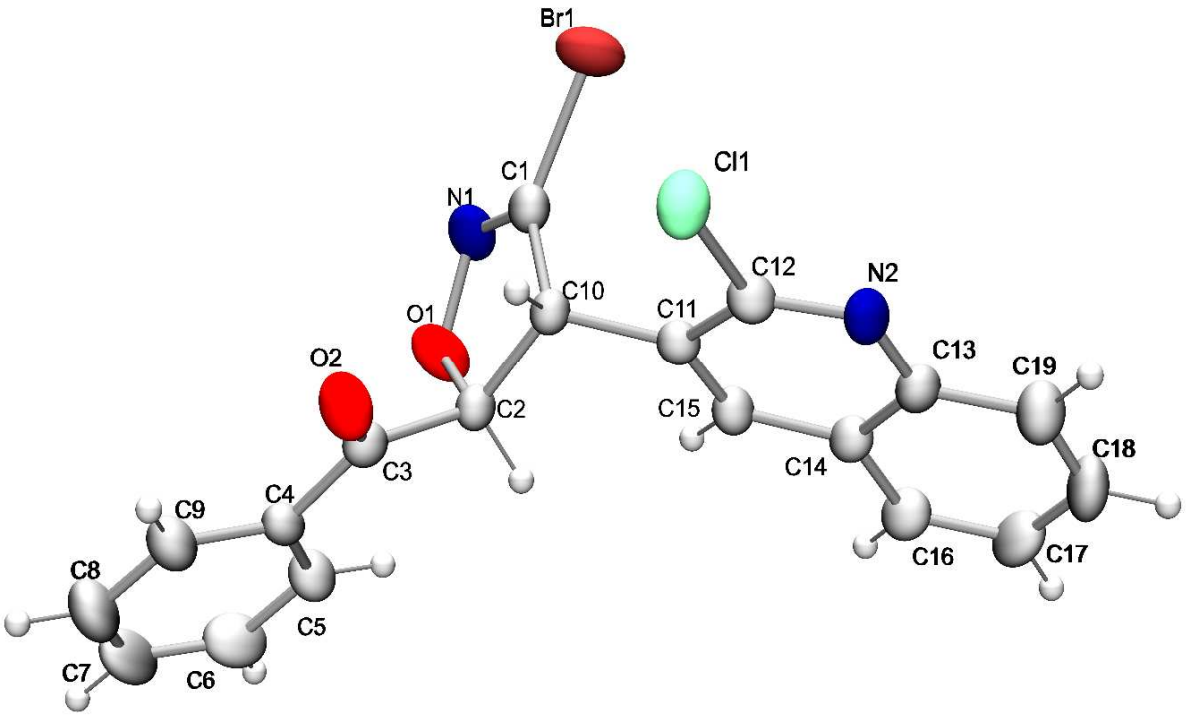
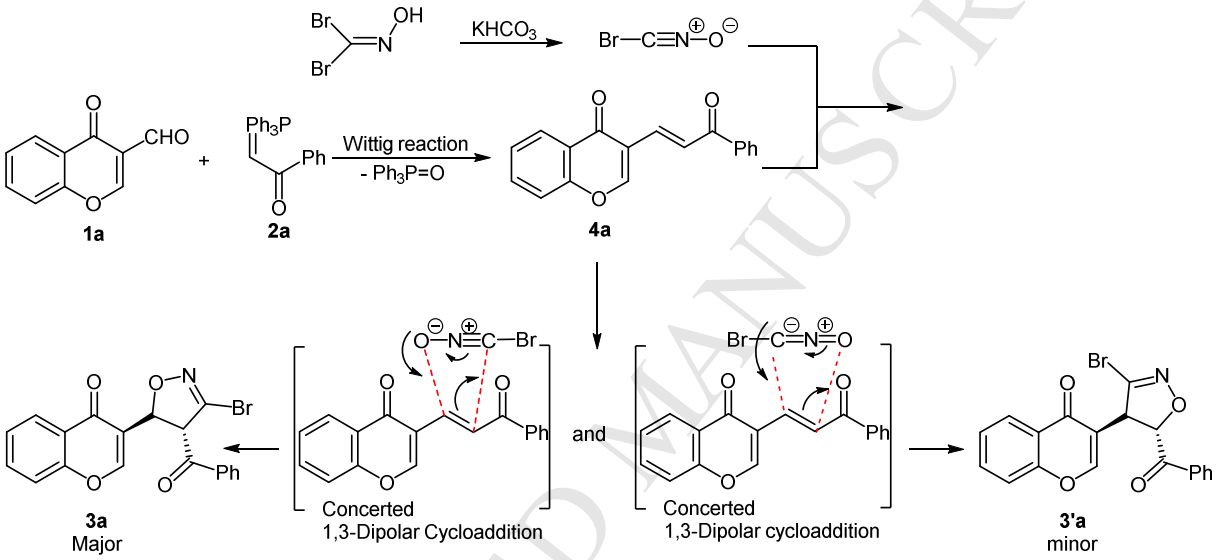


Fig. 1 ORTEP diagram of **3'f**.

A plausible mechanism for the formation of 3-(4-benzoyl-3-bromo-4,5-dihydroisoxazol-5-yl)-4*H*-chromen-4-one **3a** is depicted in Scheme 2. Initially, the Wittig reagent and the aldehyde moiety form the α,β-unsaturated compound **4a** and X-ray analysis showes that the stereochemistry of olefine intermediate **4a** is trans. Then, the *in situ* generated bromonitrile oxide undergoes [3+2] dipolar cycloaddition with the mentioned alkene **4a** to afford the corresponding 3-bromo-4,5-dihydroisoxazole **3a** and **3'a**.



Scheme 2. Mechanistic rationale for the synthesis of **3a** and **3'a**.

3. Conclusion

In summary, we have reported a rapid, simple, and efficient protocol for the synthesis of 3-bromo-4,5-dihydroisoxazole derivatives from easily available starting materials *via* 1,3-dipolar cycloaddition reactions involving bromonitrile oxide as 1,3-dipole, in a chemoselective manner. The simplicity of experimental procedure, mild, catalyst free conditions, and ready availability of starting materials, render this strategy as an attractive method for the synthesis of 3-bromo-4,5-dihydroisoxazole derivatives.

4. Experimental

All starting materials were synthesized according to the literature. Elemental analyses for C, H and N were performed using a Heraeus CHN–O–Rapid analyzer. Mass spectra were recorded on an Aglient Technologies 5975C VL MSD mass spectrometer operating at an ionization potential of 70 eV. ^{1}H NMR (500.13 MHz) and ^{13}C NMR (125 MHz) spectra were obtained using Bruker DRX-500 AVANCE spectrometers. IR spectra were recorded as KBr pellets on a NICOLET FT-IR 100 spectrometer; absorbances are reported in cm^{-1}. M. p. points were measured on an Electrothermal 9100.

4.1. General synthesis procedure (for example, 3a).

The aldehyde compound (1 mmol), 1-phenyl-2-(1,1,1-triphenyl-λ^5-phosphanylidene)ethan-1-one (1 mmol), dibromoformaldoxime (1 mmol) and $KHCO_3$ (1mmol) were combined in a vessel in DCM as solvent and the reaction mixture was stirred at room temperature for 3-5 hours. The product was obtained after purification by column chromatography on silica gel.

4.1.1. 3-(4-Benzoyl-3-bromo-4,5-dihydroisoxazol-5-yl)-4*H*-chromen-4-one (3a). Cream powder, m.p = 172-174 °C, 0.36 g, yield: 90%. IR (KBr) (ν_{max}, cm^{-1}): 1680 and 1632 (C=O), 1590 and 1464 (Ar), 1220 (C-O). Anal. Calcd. for $C_{19}H_{12}BrNO_4$ (398.21): C, 57.31; H, 3.04; N, 3.52%. Found C, 57.39; H, 3.01; N, 3.56%. MS (EI, 70 eV): *m/z* (%): 398 (3), 318 (9), 249 (6), 213 (3), 173 (13), 148 (4), 105 (100), 77.1 (40), 51.1 (9). ^{1}H NMR (500.13 MHz, $CDCl_3$) of major diastereoisomer (86 : 14): δ_H 5.42 (1H, d, $^{3}J_{HH}$ = 7.5 Hz, CH^{4}), 6.04 (1H, dd, $^{3}J_{HH}$ = 7.5 Hz, $^{4}J_{HH}$ = 1.1 Hz, CH^{5}), 7.43 (1H, t, $^{3}J_{HH}$ = 7.1 Hz, $CH^{6'}$), 7.52 (1H, d, $^{3}J_{HH}$ = 7.9 Hz, $CH^{8'}$), 7.54 (2H, t, $^{3}J_{HH}$ = 8.0 Hz, $2CH_{meta}$ of Ph), 7.66 (1H, t, $^{3}J_{HH}$ = 7.3 Hz, CH_{para} of Ph), 7.72 (1H, t, $^{3}J_{HH}$ = 7.8 Hz, $^{4}J_{HH}$ = 1.6 Hz, $CH^{7'}$), 8.08 (2H, dd, $^{3}J_{HH}$ = 7.2 Hz, $^{4}J_{HH}$ = 0.9 Hz, $2CH_{ortho}$ of Ph), 8.12 (1H, d, $^{4}J_{HH}$ = 1.1 Hz, $CH^{2'}$), 8.17 (1H, dd, $^{3}J_{HH}$ = 8.0 Hz, $^{4}J_{HH}$ = 1.6 Hz, $CH^{5'}$). ^{13}C NMR

of major and minor diastereoisomer (75.46 MHz, $CDCl_3$): δ_C 64.2 (CH^4), 82.17 (CH^5), 118.5 ($CH^{8'}$), 121.1 (C-Br), 123.8 ($C^{3'}$), 125.8 ($CH^{6'}$), 125.8 ($CH^{5'}$), 129.1 ($2CH_{meta}$ of Ph), 129.5 ($2CH_{ortho}$ of Ph), 134.5 (CH_{para} of Ph), 134.5 ($C^{4'a}$), 135.5 (C_{ipso}-C=O), 135.8 ($CH^{7'}$), 153.8 ($CH^{2'}$), 156.6 ($C^{8'a}$), 176.5 ($C^{4'}$=O), 192.9 (C=O). ^{1}H NMR (500.13 MHz, $CDCl_3$) of minor diastereoisomer (86 : 14): δ_H 5.12 (1H, d, $^3J_{HH}$ = 8.7 Hz, CH^4), 5.92 (1H, d, $^3J_{HH}$ = 8.7 Hz, CH^5), 7.43 (1H, t, $^3J_{HH}$ = 7.1 Hz, $CH^{6'}$), 7.52 (1H, d, $^3J_{HH}$ = 7.9 Hz, $CH^{8'}$), 7.54 (2H, t, $^3J_{HH}$ = 8.0 Hz, $2CH_{meta}$ of Ph), 7.65 (1H, t, $^3J_{HH}$ = 7.4 Hz, CH_{para} of Ph), 7.72 (1H, t, $^3J_{HH}$ = 7.8 Hz, $^4J_{HH}$ = 1.6 Hz, $CH^{7'}$), 8.09 (2H, dd, $^3J_{HH}$ = 8.5 Hz, $2CH_{ortho}$ of Ph), 8.03 (1H, s, $CH^{2'}$), 8.23 (1H, dd, $^3J_{HH}$ = 8.4 Hz, $^4J_{HH}$ = 1.9 Hz, $CH^{5'}$).

4.1.2. 3-(3-Bromo-4-(4-bromobenzoyl)-4,5-dihydroisoxazol-5-yl)-4*H*-chromen-4-one (3b). White powder, m.p = 184-186 °C, 0.39 g, yield 83%. IR (KBr) (ν_{max}, cm^{-1}): 1682 and 1642 (C=O), 1580 and 1465 (Ar), 1214 (C-O). Anal. Calcd. for $C_{19}H_{11}Br_2NO_4$ (477.11): C, 47.83; H, 2.32; N, 2.94%. Found C, 47.89; H, 2.30; N, 2.91%. MS (EI, 70 eV): *m/z* (%): 475 (1), 396 (3), 292 (2), 239 (2), 213 (3), 186 (1), 185.9 (11), 184.9 (96), 183 (100), 173 (21), 156.9 (25), 155 (31), 121 (14), 120 (9), 104 (13), 92 (15), 77 (9), 76 (32), 75 (25), 74 (10), 64 (9), 63 (17), 53 (12), 51 (8), 50 (22). ^{1}H NMR (500.13 MHz, $CDCl_3$): δ_H 5.32 (1H, d, $^3J_{HH}$ = 7.5 Hz, CH^4), 6.01 (1H, dd, $^3J_{HH}$ = 7.5 Hz, $^4J_{HH}$ = 1.2 Hz, CH^5), 7.43 (1H, dt, $^3J_{HH}$ = 7.6 Hz, $^4J_{HH}$ = 0.9 Hz, $CH^{6'}$), 7.51 (1H, d, $^3J_{HH}$ = 8.4 Hz, $CH^{8'}$), 7.67 (2H, t, $^3J_{HH}$ = 8.6 Hz, 2CH of Ar), 7.72 (1H, dt, $^3J_{HH}$ = 7.8 Hz, $^4J_{HH}$ = 1.6 Hz, $CH^{7'}$), 7.95 (2H, d, $^3J_{HH}$ = 8.6 Hz, 2CH of Ar), 8.11 (1H, d, $^4J_{HH}$ = 1.2 Hz, $CH^{2'}$), 8.14 (1H, dd, $^3J_{HH}$ = 8.0 Hz, $^4J_{HH}$ = 1.5 Hz, $CH^{5'}$). ^{13}C NMR (125.75 MHz, $CDCl_3$): δ_C 64.2 (CH^4), 81.9 (CH^5), 118.4 ($CH^{8'}$), 121.0 (C-Br), 123.6 ($C^{3'}$), 125.6 ($CH^{6'}$), 125.8 ($CH^{5'}$), 129.9 (C_{ipso}-Br), 130.8 (2CH of Ar), 132.3 (2CH of Ar), 134.4 ($CH^{7'}$), 134.5 ($C^{4'a}$), 135.2 (C_{ipso}-CO), 153.6 ($CH^{2'}$), 156.5 ($C^{8'a}$), 176.4 ($C^{4'}$=O), 191.9 (C=O).

4.1.3. 3-(3-Bromo-4-(4-chlorobenzoyl)-4,5-dihydroisoxazol-5-yl)-4*H*-chromen-4-one (3c). White powder, m.p = 193-195 °C, 0.38 g, yield 87%. IR (KBr) (ν_{max}, cm^{-1}): 1681 and 1629 (C=O), 1465 (Ar), 1215 (C-O). Anal. Calcd. for $C_{19}H_{11}BrClNO_4$ (432.66): C, 52.75; H, 2.56; N, 3.24%. Found C, 52.71; H, 2.59; N, 3.28%. MS (EI, 70 eV): *m/z* (%): 432 (3), 431 (11), 352 (43), 350 (35), 306 (3), 260 (12), 212 (11), 175 (1), 139 (100), 140 (10), 141 (32), 111 (40), 113 (14), 120 (8), 75 (17). ^{1}H NMR (500.13 MHz, $CDCl_3$): δ_H 5.33 (1H, d, $^3J_{HH}$ = 7.4 Hz, CH^4), 6.01 (1H, d, $^3J_{HH}$ = 7.4 Hz, CH^5), 7.43 (1H, t, $^3J_{HH}$ = 7.4 Hz, $CH^{6'}$), 7.50 (2H, t, $^3J_{HH}$ = 8.5 Hz, 2CH of Ar), 7.51 (1H, d, $^3J_{HH}$ = 7.7 Hz, $CH^{8'}$), 7.72 (1H, dt, $^3J_{HH}$ = 7.1 Hz, $^4J_{HH}$ = 1.3 Hz, $CH^{7'}$), 8.03 (1H, d, $^3J_{HH}$ = 8.5 Hz, 2CH of Ar), 8.11 (1H, s, $CH^{2'}$), 8.14 (1H, d, $^3J_{HH}$ = 7.9 Hz, $CH^{5'}$). ^{13}C NMR (125.75 MHz, $CDCl_3$): δ_C 64.2 (CH^4), 82.0 (CH^5), 118.4 ($CH^{8'}$), 121.0 (C-Br), 123.6 ($C^{3'}$), 125.6 ($CH^{6'}$), 125.7 ($CH^{5'}$), 129.3 (2CH of Ar), 130.7 (2CH of Ar), 134.1 ($C^{4'a}$), 134.4 ($CH^{7'}$), 135.2 (C_{ipso}-C=O), 141.1 (C_{ipso}-Cl), 153.6 ($CH^{2'}$), 156.5 ($C^{8'a}$), 176.4 ($C^{4'}$=O), 191.7 (C=O).

4.1.4. 3-[3-Bromo-4-(4-methylbenzoyl)-4,5-dihydroisoxazol-5-yl]-4*H*-chromen-4-one (**3d**). White powder, m.p = 179-180 °C, 0.33 g, yield 80%. IR (KBr) (ν_{max}, cm^{-1}): 1646 and 1607 (C=O), 1463 and 1590 (Ar), 1251 (C-O). Anal. Calcd. for $C_{20}H_{14}BrNO_4$ (412.24): C, 58.27; H, 3.42; N, 3.40%. Found C, 58.20; H, 3.49; N, 3.45%. MS (EI, 70 eV): *m/z* (%): 332 (2), 213 (3), 183 (6), 173 (19), 171 (4), 155 (4), 146 (7), 127 (4), 121 (10), 120 (25), 119 (100), 104 (5), 93 (2), 92 (11), 91 (47), 90 (5), 89 (9), 77 (3), 65 (15), 64 (4), 63 (8), 53 (3). ^{1}H NMR (500.13 MHz, $CDCl_3$): δ_H 2.41 (3H, s, Me), 541 (1H, d, $^3J_{HH}$ = 7.5 Hz, CH^4), 6.01 (1H, dd, $^3J_{HH}$ = 7.5 Hz, $^4J_{HH}$ = 1.0 Hz, CH^5), 7.32 (2H, d, $^3J_{HH}$ = 8.1 Hz, 2CH of Ar), 7.42 (1H, dt, $^3J_{HH}$ = 7.6 Hz, $^4J_{HH}$ = 0.9 Hz, $CH^{6'}$), 7.50 (1H, d, $^3J_{HH}$ = 8.4 Hz, $CH^{8'}$), 7.71 (1H, dt, $^3J_{HH}$ = 7.8 Hz, $^4J_{HH}$ = 1.6 Hz, $CH^{7'}$), 7.96 (2H, d, $^3J_{HH}$ = 8.2 Hz, 2CH of Ar), 8.09 (1H, d, $^4J_{HH}$ = 1.0 Hz, $CH^{2'}$), 8.16 (1H, dd, $^3J_{HH}$ = 8.0 Hz, $^4J_{HH}$ = 1.5 Hz, $CH^{5'}$). ^{13}C NMR (125.75 MHz, $CDCl_3$): δ_C 21.8 (Me), 63.9 (CH^4), 82.1 (CH^5), 118.3 ($CH^{8'}$), 121.0 (C-Br), 123.8 ($C^{3'}$), 125.7 ($CH^{6'}$ and $CH^{5'}$), 129.5 (2CH of Ar), 129.7

(2CH of Ar), 133.2 ($C^{4'a}$), 134.3 ($CH^{7'}$), 135.6 (C_{ipso}-C=O), 145.6 (*C*-Me), 153.8 ($CH^{2'}$), 156.4 ($C^{8'a}$), 176.3 ($C^{4'}$=O), 192.2 (C=O).

4.1.5. 3-(4-Benzoyl-3-bromo-4,5-dihydroisoxazol-5-yl)-6-chloro-4*H*-chromen-4-one (**3e**). White powder, m.p = 153-154 °C, 0.38 g, yield 87%. IR (KBr) (ν_{max}, cm^{-1}): 1682 and 1639 (C=O), 1456 (Ar), 1212 (C-O). Anal. Calcd. for $C_{19}H_{11}BrClNO_4$ (432.66): C, 52.75; H, 2.56; N, 3.24%. Found C, 52.71; H, 2.50; N, 3.29%. MS (EI, 70 eV): *m/z* (%): 432 (1), 351 (3), 247 (2), 217 (2), 209 (3), 207 (9), 180 (3), 155 (4), 154 (4), 126 (7), 105 (100), 106 (14), 89 (3), 78 (4), 75 (3), 63 (7), 53 (5), 51 (13), 50 (4). ^{1}H NMR (500.13 MHz, $CDCl_3$): δ_H 5.37 (1H, d, $^3J_{HH}$ = 7.5 Hz, CH^4), 6.04 (1H, d, $^3J_{HH}$ = 7.5 Hz, CH^5), 7.48 (1H, d, $^3J_{HH}$ = 8.9 Hz, $CH^{8'}$), 7.54 (2H, t, $^3J_{HH}$ =7.6 Hz, $2CH_{meta}$ of Ph), 7.64-7.69 (2H, m, CH_{para} of Ph and $CH^{7'}$), 8.06 (2H, d, $^3J_{HH}$ = 8.0 Hz, $2CH_{ortho}$ of Ph), 8.11 (1H, d, $^4J_{HH}$ = 2.5 Hz, $CH^{2'}$), 8.12 (1H, s, $CH^{5'}$). ^{13}C NMR (125.75 MHz, $CDCl_3$): δ_C 64.1 (CH^4), 81.8 (CH^5), 120.1 ($CH^{8'}$), 121.3 (C-Br), 124.6 ($C^{3'}$), 125.1 ($CH^{5'}$), 129.0 ($2CH_{meta}$ of Ph), 129.3 ($2CH_{ortho}$ of Ph), 131.8 ($C^{6'}$), 134.4 ($CH^{7'}$), 134.6 (CH_{para} of Ph), 135.5 ($C^{4'a}$), 135.7 (C_{ipso}-CO), 153.8 ($CH^{2'}$), 154.8 ($C^{8'a}$), 175.2 ($C^{4'}$=O), 192.6 (C=O).

4.1.6. [3-bromo-4-(2-chloroquinolin-3-yl)-4,5-dihydroisoxazol-5-yl](phenyl)methanone (3'f). White powder, m.p = 138-140 °C, 0.35 g, yield 85%, IR (KBr) (ν_{max}, cm^{-1}): 1685 (C=O), 1587 and 1449 (Ar), 1234 (C-O). Anal. Calcd. for $C_{19}H_{12}BrClN_2O_2$ (415.67): C, 54.90; H, 2.91; N, 6.74%. Found C, 54.95; H, 2.96; N, 6.70%. MS (EI, 70 eV): *m/z* (%):415 (2), 311 (2), 202 (2), 201 (2), 192 (4), 191 (2), 190 (11), 166 (4), 165 (3), 164 (2), 162 (2), 140 (4), 139 (4), 127 (3), 113 (2), 106 (18), 105 (100), 101 (2), 78 (3), 77 (41), 75 (3), 63 (2), 51 (11), 50 (3). ^{1}H NMR (500.13 MHz, $CDCl_3$) of major isomer (32 : 68): δ_H 5.21 (1H, d, $^3J_{HH}$ = 7.0 Hz, $CH^{4'}$), 5.85 (1H, d, $^3J_{HH}$ = 7.0 Hz, $CH^{5'}$), 7.50 (2H, t, $^3J_{HH}$ = 7.8 Hz, $2CH_{meta}$ of Ph), 7.68 (1H, t, $^3J_{HH}$ = 7.3 Hz, CH_{para} of Ph), 7.77 (1H, d, $^3J_{HH}$ = 8.5 Hz, CH^5), 7.80 (1H, d, $^3J_{HH}$ = 8.2 Hz, CH^8), 7.87 (2H, t, $^3J_{HH}$ = 7.8 Hz, CH^6 and CH^7), 8.06 (2H, d, $^3J_{HH}$ = 7.6 Hz, $2CH_{ortho}$ of Ph), 8.12 (1H, s, CH^4). ^{13}C

NMR of major isomer (125.75 MHz, $CDCl_3$): δ_C 66.1 ($CH^{4'}$), 84.2 ($CH^{5'}$), 127.1 (C^{4a}), 127.7 (CH^6), 127.9 (CH^8), 128.4 (CH^5), 128.9 ($2CH_{meta}$ of Ph), 129.7 ($2CH_{ortho}$ of Ph), 130.5 (C^3), 131.5 (CH^7), 133.8 (C-Br), 134.5 (CH_{para} of Ph), 136.2 (CH^4), 139.8 (C_{ipso} of Ph), 147.5 (C^{8a}), 149.4 (C-Cl), 190.8 (C=O). Crystal data for **3'f** $C_{19}H_{12}BrClN_2O_2$ (CCDC 1574900): M_W = 415.56, orthorhombic, P b c a, a = 10.485(2) Å, b = 14.400(3) Å, c = 23.012(5) Å, α = 90.00, β = 90.00, γ = 90.00, V = 3474.4(12) $Å^3$, Z = 8, Dc = 1.589 mg/m^3, F (000) = 1664, crystal dimension 0.35 × 0.263 × 0.2 mm, radiation, Mo Kα (λ = 0.71073 Å), $1.77 \leq 2\theta \leq 26.85$, intensity data were collected at 293(2) K with a Bruker APEX area-detector diffractometer, and employing $\omega/2\theta$ scanning technique, in the range of $-12 \leq h \leq 11$, $-17 \leq k \leq 17$, $-27 \leq l \leq 27$; the structure was solved by a direct method, all non-hydrogen atoms were positioned and anisotropic thermal parameters refined from 3066 observed reflections with R (into) = 0.1067 by a full-matrix least-squares technique converged to R = 0.0386 and Raw = 0.0606 [I>2sigma(I)]. ^{1}H NMR of minor isomer (500.13 MHz, $CDCl_3$): δ_H 5.84 (1H, d, $^3J_{HH}$ = 5.9 Hz, $CH^{4'}$), 6.45 (1H, d, $^3J_{HH}$ = 5.9 Hz, $CH^{5'}$), 7.53 (2H, t, $^3J_{HH}$ = 7.6 Hz, $2CH_{meta}$ of ph), 7.60-7.64 (3H, m, CH_{para} of Ph and CH^6 and CH^7), 8.00 (1H, d, $^3J_{HH}$ = 8.4 Hz, CH^5), 8.03 (1H, d, $^3J_{HH}$ = 8.4 Hz, CH^8), 8.04 (2H, d, $^3J_{HH}$ = 7.6 Hz, $2CH_{ortho}$ of Ph), 8.39 (1H, s, CH^4). ^{13}C NMR of minor isomer (125.75 MHz, $CDCl_3$): δ_C 56.7 ($CH^{4'}$), 87.7 ($CH^{5'}$), 126.9 (C^{4a}), 127.8 (CH^6), 128.1 (CH^8), 128.3 (CH^5), 129.1 ($2CH_{meta}$ of Ph), 129.3 ($2CH_{ortho}$ of Ph), 131.2 (CH^7), 133.5 (C^3), 134.8 (CH_{para} of Ph), 135.2 (C-Br), 136.2 (CH^4), 139.0 (C_{ipso} of Ph), 147.1 (C-Cl), 147.5 (C^{8a}), 192.1 (C=O).

4.1.7. [3-Bromo-5-(2-chloroquinolin-3-yl)-4,5-dihydroisoxazol-4-yl](4-bromophenyl)methanone (3g). White powder, m.p = 155-157 °C, 0.37 g, yield 87%, IR (KBr) (ν_{max}, cm^{-1}): 1682 (C=O), 1580 and 1487 (Ar), 1256 (C-O). Anal. Calcd. for $C_{19}H_{11}Br_2ClN_2O_2$ (494.57): C, 46.14; H, 2.24; N, 5.66%. Found C, 46.10; H, 2.29; N, 5.61%. MS (EI, 70 eV): 494 (1), 457 (4), 415 (1), 378 (6), 376 (6), 311 (3), 275 (1), 241 (1), 202 (4), 201 (3), 200 (4), 192

(10), 191 (5), 190 (31), 186 (9), 185 (97), 184 (9), 183 (100), 167 (4), 166 (7), 165 (7), 164 (7), 162 (10), 157 (25), 155 (27), 149 (5), 143 (3), 140 (6), 139 (5), 138 (3), 128 (3), 127 (10), 126 (4), 114 (3), 113 (3), 104 (4), 101 (7), 76 (14), 75 (12), 74 (4), 50 (6). ^{1}H NMR (500.13 MHz, $CDCl_3$) of major diastereoisomer (72 : 28): δ_H 5.14 (1H, d, $^{3}J_{HH}$ = 6.0 Hz, $CH^{4'}$), 6.44 (1H, d, $^{3}J_{HH}$ = 6.0 Hz, $CH^{5'}$), 7.64 (1H, t, $^{3}J_{HH}$ = 7.8 Hz, CH^{7}), 7.66 (1H, d, $^{3}J_{HH}$ = 8.5 Hz, CH^{5}), 7.69 (2H, d, $^{3}J_{HH}$ = 8.5 Hz, 2CH of Ar), 7.79 (1H, t, $^{3}J_{HH}$ = 8.3 Hz, CH^{6}), 7.91 (2H, d, $^{3}J_{HH}$ = 8.5 Hz, 2CH of Ar), 8.02 (1H, d, $^{3}J_{HH}$ = 8.4 Hz, CH^{8}), 8.40 (1H, s, CH^{4}). ^{13}C NMR of major diastereoisomer (125.75 MHz, $CDCl_3$): δ_C 66.1 (CH4'), 84.2 ($CH^{5'}$), 126.9 ($C^{3'}$-Br), 127.9 (CH^{6}), 128.1 (CH^{8}), 128.3 (CH^{5}), 128.3 (C_{ipso}-Br), 130.5 (C^{3}), 131.3 (CH^{7}), 132.1 (C4a), 132.5 (2CH of Ar), 133.9 (C_{ipso}-C=O), 136.2 (CH4), 146.9 (C^{8a}), 147.5 (C-Cl), 191.2 (C=O). ^{1}H NMR (500.13 MHz, $CDCl_3$) of minor diastereoisomer(72 : 28): δ_H 5.79 (1H, d, $^{3}J_{HH}$ = 5.2 Hz, $CH^{4'}$), 5.83 (1H, d, $^{3}J_{HH}$ = 5.5 Hz, $CH^{5'}$), 7.53 (1H, d, $^{3}J_{HH}$ = 8.5 Hz, CH^{5}), 7.64 (1H, t, $^{3}J_{HH}$ = 7.8 Hz, CH^{7}), 7.69 (2H, d, $^{3}J_{HH}$ = 8.5 Hz, 2CH of Ar), 7.79 (1H, t, $^{3}J_{HH}$ = 8.3 Hz, CH^{6}), 7.90 (2H, d, $^{3}J_{HH}$ = 8.7 Hz, 2CH of Ar), 8.05 (1H, d, $^{3}J_{H\text{-}H}$ = 8.6 Hz, CH^{8}), 8.10 (1H, s, CH^{4}). ^{13}C NMR of minor diastereoisomer (125.75 MHz, $CDCl_3$): δ_C 56.6 ($CH^{4'}$), 87.6 ($CH^{5'}$), 127.1 ($C^{3'}$), 127.6 (CH^{5}), 128.0 (CH^{6}), 128.4 (CH^{8}), 128.7 (C_{ipso}-Br), 130.0 (C^{3}), 131.2 (2CH of Ar), 131.5 (CH^{7}), 132.3 ($2CH_{ortho}$ of Ar), 132.2 (C^{4a}), 132.9 (C_{ipso}-C=O), 133.1 (CH^{4}), 147.5 (C^{8a}), 149.3 (C^{2}), 190.0 (C=O).

4.1.8. (3-Bromo-5-[1,2,3,4]tetrazolo[1,5-*a*]quinolin-4-yl-4,5-dihydroisoxazol-4-yl)(phenyl)methanone (**3h**). White powder, m.p = 190 °C, 0.33 g, yield 80%, IR (KBr) (ν_{max}, cm^{-1}): 1683 (C=O), 1614 (C=N), 1532 and 1448 (Ar), 1220 (C-O). Anal. Calcd. for $C_{19}H_{12}BrN_5O_2$ (422.24): C, 54.05; H, 2.86; N, 16.59%. Found C, 54.09; H, 2.81; N, 16.51%. MS (EI, 70 eV): *m/z* (%): 422 (0.1), 343 (3), 342 (13), 314 (3), 297 (3), 296 (2), 283 (3), 256 (2), 255 (2), 218 (1), 197 (2), 179 (4), 170 (6), 154 (5), 153 (3), 152 (6), 151 (2), 143 (8), 142 (8), 141

(11), 140 (3), 129 (2), 128 (4), 127 (6), 126 (2), 125 (3), 116 (5), 115 (21), 114 (14), 113 (3), 106 (25), 105 (100), 101 (4), 100 (2), 90 (3), 89 (8), 88 (7), 87 (4), 78 (9), 77 (87), 76 (7), 75 (6), 74 (4), 64 (3), 63 (8), 62 (4), 52 (3), 51 (22), 50 (7). ^{1}H NMR (500.13 MHz, $CDCl_3$): δ_H 5.81 (1H, d, $^{3}J_{HH}$ = 6.9 Hz, $CH^{4'}$), 6.60 (1H, dd, $^{3}J_{HH}$ = 6.9 Hz, $^{4}J_{HH}$ = 2.7 Hz, $CH^{5'}$), 7.54 (2H, t, $^{3}J_{HH}$ = 6.8 Hz, $2CH_{meta}$ of Ph), 7.68 (1H, t, $^{3}J_{HH}$ = 6.7 Hz, CH_{para} of Ph), 7.77 (1H, t, $^{3}J_{HH}$ = 7.3 Hz, CH^{6}), 7.93 (1H, t, $^{3}J_{HH}$ = 7.3 Hz, CH^{7}), 8.04 (1H, d, $^{3}J_{HH}$ = 7.7 Hz, CH^{5}), 8.11 (2H, d, $^{3}J_{HH}$ = 7.6 Hz, $2CH_{ortho}$ of Ph), 8.17 (1H, s, CH^{4}), 8.70 (1H, dd, $^{3}J_{HH}$ = 8.3 Hz, $^{4}J_{HH}$ = 2.7 Hz, CH^{8}). ^{13}C NMR (125.75 MHz, $CDCl_3$): δ_C 63.8 ($CH^{4'}$), 82.8 ($CH^{5'}$), 116.4 (CH^{8}), 122.2 (C-Br), 128.1 (CH^{6}), 128.2 (C^{4a}), 128.6 ($2CH_{meta}$ of Ph), 129.1 ($2CH_{ortho}$ of Ph and CH^{5}), 130.1 (C^{3}), 130.6 (CH^{7}), 131.4 (CH^{4}), 134.3 (CH_{para} of Ph), 134.3 (C^{8a}), 134.7 (C_{ipso} of Ph), 146.0 (C^{2}), 191.6 (C=O).

4.1.9. (3-Bromo-5-[1,2,3,4]tetrazolo[1,5-*a*]quinolin-4-yl-4,5-dihydroisoxazol-4-yl)(4-methylphenyl)methanone (3i). White powder, m.p = 178-179 °C, 0.37 g, yield 85%, IR (KBr) (ν_{max}, cm^{-1}): 1674 (C=O), 1607 (C=N), 1534 and 1460 (Ar), 1260 (C-O). Anal. Calcd. for $C_{20}H_{14}BrN_5O_2$ (436.27): C, 55.06; H, 3.23; N, 16.05%. Found C, 55.01; H, 3.29; N, 16.01%. MS (EI, 70 eV): *m/z* (%): 436 (0.1), 356 (5), 354 (4), 326 (5), 325 (4), 298 (2), 297 (2), 259 (3), 231 (4), 179 (3), 170 (3), 157 (4), 154 (3), 152 (4), 142 (5), 141 (8), 140 (4), 130 (3), 127 (5), 120 (21), 119 (100), 116 (3), 115 (12), 114 (10), 101 (3), 92 (6), 91 (62), 89 (10), 65 (21), 63 (9), 51 (5). ^{1}H NMR (500.13 MHz, $CDCl_3$): δ_H 5.79 (1H, d, $^{3}J_{HH}$ = 7.0 Hz, $CH^{4'}$), 6.57 (1H, d, $^{3}J_{HH}$ = 7.0 Hz, $CH^{5'}$), 7.32 (2H, d, $^{3}J_{HH}$ = 8.0 Hz, 2CH of Ar), 7.76 (1H, t, $^{3}J_{HH}$ = 7.5 Hz, CH^{6}), 7.92 (1H, t, $^{3}J_{HH}$ = 7.6 Hz, CH^{7}), 7.99 (2H, d, $^{3}J_{HH}$ = 8.2 Hz, 2CH of Ar), 8.03 (1H, d, $^{3}J_{HH}$ = 7.9 Hz, CH^{5}), 8.15 (1H, s, CH^{4}), 8.68 (1H, d, $^{3}J_{HH}$ = 8.3 Hz, CH^{8}). ^{13}C NMR (125.75 MHz, $CDCl_3$): δ_C 21.8 (Me), 64.04 ($CH^{4'}$), 83.3 ($CH^{5'}$), 116.8 (CH^{8}), 122.7 (C-Br), 128.5 (CH^{6}), 128.7 (C^{4a}), 129.5 (CH^{5}), 129.7 ($2CH_{meta}$ of Ar), 129.7 ($2CH_{ortho}$ of Ar), 130.3 (C^{3}), 131.1 (CH^{7}), 131.8 (CH^{4}), 134.1 (C^{8a}), 135.3 (C_{ipso}-C=O), 145.4 (C_{ipso}-Me), 146.0 (C^{2}), 191.4 (C=O).

References

1. (a) Joule J A, Mills K *Heterocyclic Chemistry*, 5th ed.; Wiley: Chichester, UK, 2010. (b) Katritzky A R, Ramsden C A, Joule J A, Zhdankin V V Handbook of Heterocyclic Chemistry, 3rd ed.; Elsevier: Oxford, 2010. (c) Dua R, Shristava S, Sonwane S K, Srivastava S R *Adv. Biol. Res.* 2011; 3:120. (d) Sperry J B, Wright D L *Curr. Opin. Drug Discovery Dev.* 2005; 8:723. (e) Riego E, Hernandez D, Albericio F, Alvarez M *Synthesis* 2005; 1907. (f) Broughton H B, Watson I A *J. Mol. Graphics Modell.* 2004; 23:51.
2. Grünanger P, Vita-Finzi P In The Chemistry of Heterocyclic Compounds; Taylor, E C, Ed.; J. Wiley and Sons: New York, 1991; 49:572.
3. (a) Kozikowski A P, Adamczyk M *Tetrahedron Lett.* 1982, 23:3123. (b) Curran D P *J. Am. Chem. Soc.* 1983; 105:5826. (c) Curran D P, Scanga S A, Fenk C J *J. Org. Chem.* 1984; 49:3474.
4. Lee S Y, Lee B S, Lee C-W, Oh D Y *J. Org. Chem.* 2000; 65:256.
5. Kozikowski A P *Acc. Chem. Res.* 1984; 17:410.
6. Yashiro A, Nishida Y, Kobayashi K, Ohno M *Synlett* 2000; 361.
7. Mizabuchis Satoy *Agri. Bio. Chem.* 1984; 48:2771.
8. Bhakunin D. S, Chaturvedi R J. *Nat. Prod.* 1984; 47:585.
9. Shivkumar B, Nargund L V G *Indian J. Heterocyclic Chem.* 1998; 8:27.
10. Vittorio F, Ronsisvalle G, Pappalardo M S, Blandino G *Chem. Abstr.* 1985; 103:19721.
11. Nagano M, Sakai J, Mizukai M, Nakamura N, Misaka E, Kobayashi S, Tomita K, Kokai I *Chem. Abstr.* 1979; 92:41922.
12. Ichiba T, Scheuer P J *J. Org. Chem.* 1993; 58;4149.
13. Pinto J P D *J. Med. Chem.* 2001; 44:566.
14. Bhosale S, Kurhade S, Prasad U V, Palle V P, Bhuniya D *Tetrahedron Lett.* 2009; 50:3948.

15. (a) Yoo K H, Choi E B, Lee H K, Yeon G H, Yang H C, Pak C S *Synthesis* 2006, 1599. (b) Popp F D *Eur. J. Med. Chem.* 1989; 24:313. (c) Hino K, Nagai Y, Uno H *Chem. Pharm. Bull.* 1987; 35:2819. (d) Bajwa G S, Hartman K E, Joullie M M *J. Med. Chem.* 1973; 16:134. (e) Eswaran S.; Adhikari A V, Shetty N S *Eur. J. Med. Chem.* 2009; 44:4637.

16. (a) Pandey G, Banerjee P, Gadre S. R *Chem. Rev.* 2006; 106:4484. (b) Gothelf K V, Jørgensen K A *Chem. Rev.* 1998; 98:863. (c) Mita T, Ohtsuki N, Ikeno T, Yamada T. *Org. Lett.* 2002; 4:2457. (d) Stephens B E, Liu, F *J. Org. Chem.* 2009; 74:254. (e) Legeay J. C, Langlois, N *J. Org. Chem.* **2007**; 72:10108. (f) Oppolzer W, Weber H P *Tetrahedron Lett.* 1970; 11:1121. (g) Busque F, de March P, Figueredo M, Font J, Monsalvatje M, Virgili A, Alvarez-Larena A, Piniella J F *J. Org. Chem.* 1996: 61:8578. (h) Coldham I, Hufton R *Chem. Rev.* 2005; 105:2765.

17. Abdolali A, Roosta A *Synlett* 2016; 27:2455.

18. Abdolali A, Bayat F *Helv. Chim. Acta.* 2014; 97:694.

19. El-Subbagh H. I., Abu-Zaid S. M., Mahran M. A., Badria F. A., Alofaid A. M. *J. Med.Chem.* 2000; 43:2915.

20. Gupta R., Gupta A. K., Paul S. *Ind. J. Chem.* 2000; 39(B):847.

21. Kumar P., Knaus E. E. *Drug Des. Discov.* 1994; 11:15.

22. Dereu N.; Evers M.; Poujade C.; Soler F. PCT Int. Appl. WO 9426725, (1994); C.A., 122, 214297p (1995).

23. Shukla J. S., Saxena S. *Indian Drugs* 1980; 18:15.

24. Shekarchi M.; Marvasti, M. B., Sharifzadeh M.,Shafiee A. *Iran. J. Pharm. Res.* 2005; 1:33.

25. (a) Adamec J, Beckert R, Weib D. et al. *Bioorg. Med. Chem.* 2007; 15:2898. (b) Pluta K, Morak-Mlodawska B, Jelen M. Eur. *J. Med. Chem.* 2011; 46:3179.

26. (a) Gupta R., Gupta A. K., Paul S. *Indian J. Chem.* 2000; 44(B):847. (b) Bekhit A A, El-Sayed O A, Aboulmagd E. et al. Eur. *J. Med. Chem.* 2004; 39:249. (c) Bekhit A A, El-Sayed O A, Al-Allaf T. A. K. et al. *Eur. J. Med. Chem.* 2004; 39:499.

27. (a) La´cova´ M, Stankovicˇova´ H, Odlerova´ Zˇ. *Farmaco* 1995; 50:885. (b) El-Shaaer H. M, Foltı´nova´ P, La´cova´ M, Chovancova´ J, Stankovicˇova´ H *Farmaco* 1998; 53:224. (c) Kayser O, Kolodziej H Z *Naturforsch.* 1999; 54:169.

28. (a) Ishar, M P S, Singh G, Singh S, Sreenivasan K K, Singh G. *Bioorg. Med.Chem. Lett.* 2006; 16:1366. (b) Nawrot-Modranka J, Nawrot E, Graczyk J. *Eur. J. Med. Chem.* 2006; 41:1301. (c) Valenti P, Fabbri G, Rampa A, Bisi A, Gobbi S, Da Re P, Carrara M, Sgevano A, Cima L. *Anticancer Drug Des.* 1996; 11:243.

29. (a) Kirkiacharian S, Thuy D T, Sicsic S, Bakhchinian R, Kurkijan R, Tonnaire T Farmaco 2002; 57:703. (b) Mao P C-M, Mouscadet J F, Leh H, Auclair C, Hsu L Y *Chem. Pharm. Bull.* 2002; 50:1634.