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Molecular iodine catalyzed synthesis of tetrazolo[1,5-*a*]-quinoline based imidazoles as a new class of antimicrobial and antituberculosis agents

Divyesh C. Mungra, Harshad G. Kathrotiya *, Niraj K. Ladani, Manish P. Patel, Ranjan G. Patel

Department of Chemistry, Sardar Patel University, Vallabh Vidyanagar 388120, India

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Abstract

A series of some new tetrazolo[1,5-*a*]quinoline based tetrasubstituted imidazole derivatives **6a–l** have been synthesized by a reaction of tetrazolo[1,5-*a*]quinoline-4-carbaldehyde **3a–d**, benzil **4**, aromatic amine **5a–c** and ammonium acetate in the presence of iodine through one-pot multi-component reaction (MCR) approach. All the derivatives were screened for antimicrobial and antituberculosis activities and results worth further investigations.

Keywords: Tetrazolo[1,5-*a*]quinoline; Imidazole; MCR; Iodine; Antimicrobial activity; Antituberculosis activity

The imidazole ring system is considered to be one of the most imperative heterocyclic substructures found in a large number of natural products and pharmacologically active compounds. An examination of literature revealed that imidazole and their analogues usually possess diverse biological activities like antimicrobial, antioxidant, anti-hemolytic, cytotoxic [1], antimycobacterial [2], *etc.* On the other hand, the quinoline derivatives are also well known for their various types of biological activities such as antimicrobial [3], antiproliferative [4], antimycobacterial [5], anticancer [6], anti-HIV [7], anticoccidial [8], insecticidal [9], antidyslipidemic and antioxidative [10].

The tetrazole group has considered analogous to carboxylic group [11] as a pharmacophore. Several substituted tetrazoles show pronounced activities including antimicrobial, antimycobacterial, antiproliferative, anticancer and multi-drug resistance, *etc.* [12]. The most prominent pharmaceutical application of tetrazoles is as angiotensin II receptor antagonists for the treatment of high-blood pressure [13]. The fusion of quinoline to the tetrazole ring is known to increase the biological activity [14]. In particular, tetrazolo[1,5-*a*]quinoline-4-carbaldehyde serves as a key synthetic intermediate for the synthesis of novel medicinally valuable compounds [15]. Encouraged by their potential clinical applications and in continuation of our previous investigations on biopotent heterocycles [16], our efforts are focused to design and synthesize more biologically potent heterocyclic systems *via* combination of diverse therapeutically active moieties quinoline, tetrazole and imidazole together in a single scaffold.

* Corresponding author.
E-mail address: harshad_kathrotiya@yahoo.com (H.G. Kathrotiya).

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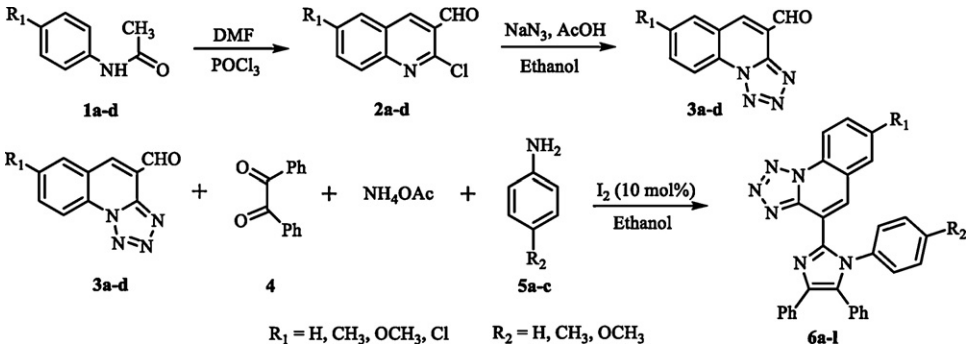


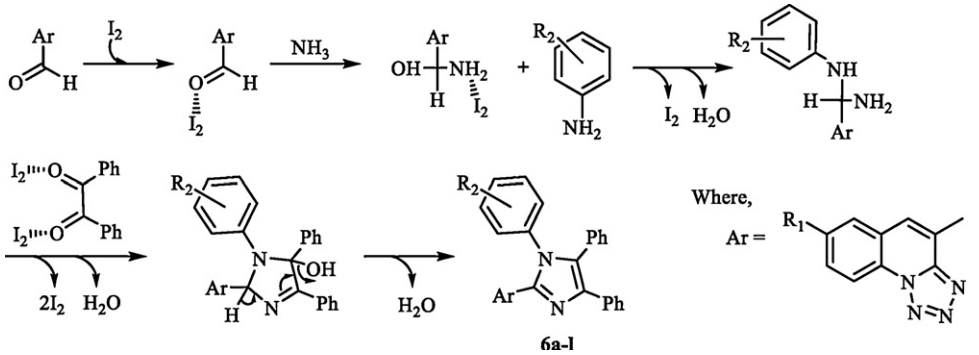
Scheme 1. General synthetic route for the synthesis of title compounds **6a–l**.

Various methods for the synthesis of multi-substituted imidazole derivatives involving different catalysts including $AlCl_3$, $FeCl_3$, $Yb(OTf)_3$, $NdCl_3$, $LaCl_3$ [17], $ZrOCl_2{\cdot}8H_2O$ [18], $BF_3{\cdot}SiO_2$, zeolite [19], NaH_2PO_4 [20], cyclic phosphoric acid [21], SiO_2 [22], *etc.* are available but not a single report has been found where tetrazolo[1,5-*a*]quinoline-4-carbaldehyde is used for the synthesis of 1,2,4,5-tetrasubstituted imidazole derivatives using I_2 as catalyst. Also, the most suitable protocol for the synthesis of functionalized organic compounds would be a one-pot reaction due to the fact that the synthesis can be performed without the isolation of the intermediates, without discharging any functional groups and within shorter reaction time [23]. Thus, in a view to obtain more biologically potent heterocyclic system, containing both therapeutically active moieties quinoline and imidazole, we report herein the synthesis of novel imidazole analogues bearing tetrazolo[1,5-*a*]quinoline nucleus *via* MCR approach.

The imidazoles **6a–l** were synthesized using iodine catalyst with good yield (76–85%). While optimizing, the yield was very poor without catalyst. Presence of iodine in the reaction revealed good yield. Moreover, equivalence optimization for best yield concluded to use just 10% of iodine in reaction. The key intermediate, tetrazolo[1,5-*a*]quinoline-4-carbaldehyde **3a–d** were synthesized by refluxing 2-chloroquinoline-3-carbaldehyde **2a–d**, sodium azide and acetic acid in ethanol according to our literature procedure [24]. 2-Chloroquinoline-3-carbaldehydes **2a–d** were synthesized according to literature procedure [25]. In present study, 1,2,4,5-tetrasubstituted imidazole derivatives **6a–l** have been synthesized by a reaction of tetrazolo[1,5-*a*]quinoline-4-carbaldehyde **3a–d**, benzil **4**, aromatic amine **5a–c**, ammonium acetate in the presence of iodine (Scheme 1).

Molecular iodine is capable of binding with the carbonyl oxygen increasing the reactivity of the parent carbonyl compound. Iodine facilitates the formation of the diimine intermediate, which under mild acid catalysis of I_2 condenses further with the carbonyl carbon of the 1,2-diketone and subsequent elimination of water affords imidazoles **6a–l** (Scheme 2).

The structures of all the new synthesized compounds were established by ^1H NMR, ^{13}C NMR, FTIR, mass and elemental analysis. The physicochemical and spectral properties of molecules of interests, compound **6h** and **6l** are



Scheme 2. Plausible mechanistic pathway for the synthesis of title compounds **6a–l**.

Table 1
Antimicrobial and antituberculosis activities of title compounds (**6a–l**).

Compd.	R_1	R_2	Minimum inhibitory concentration (MIC, μg/mL)							
			Gram-positive bacteria		Gram-negative bacteria		Fungal species		Antituberculosis activity	
			S.P.	B.S.	S.T.	E.C.	A.F.	C.A.	% inhibition	M. tb H37Rv
6a	H	H	250	200	250	250	>1000	500	80	–
6b	CH_3	H	200	200	250	200	>1000	>1000	33	–
6c	OCH_3	H	250	500	125	250	1000	500	42	–
6d	Cl	H	62.5	100	100	62.5	500	200	97	100
6e	H	CH_3	200	125	250	250	1000	500	58	–
6f	CH_3	CH_3	250	500	250	100	100	1000	95	125
6g	OCH_3	CH_3	62.5	100	200	100	>1000	1000	40	–
6h	Cl	CH_3	25	62.5	62.5	62.5	>1000	250	99	25
6i	H	OCH_3	250	125	250	125	>1000	500	17	–
6j	CH_3	OCH_3	100	250	100	100	1000	500	45	–
6k	OCH_3	OCH_3	250	200	125	125	1000	>1000	81	–
6l	Cl	OCH_3	50	100	62.5	100	>1000	250	98	62.5
Ampicillin			100	250	100	100	–	–	–	–
Norfloxacin			10	100	10	10	–	–	–	–
Ciprofloxacin			50	50	25	25	–	–	–	–
Chloramphenicol			50	50	50	50	–	–	–	–
Griseofulvin			–	–	–	–	100	500	–	–
Nystatin			–	–	–	–	100	100	–	–
Refampicin			–	–	–	–	–	–	98	40
Isoniazid			–	–	–	–	–	–	99	0.20

S.P., *Streptococcus pneumoniae*; B.S., *Bacillus subtilis*; S.T., *Salmonella typhi*; E.C., *Escherichia coli*; A.F., *Aspergillus fumigatus*; C.A., *Candida albicans*; M. tb H37Rv, *Mycobacterium tuberculosis* H37Rv; '–' represents 'not tested'.

presented in Ref. [26]. The target compounds were evaluated for their *in vitro* antimicrobial activity using broth microdilution method according to National Committee for Clinical Laboratory Standards (NCCLS) [27].

The examination of antimicrobial activity data, it has been observed that compounds **6d**, **6g**, **6h** and **6l** showed excellent activity against gram positive bacteria *S. pneumonia* compared to reference drugs. In case of inhibiting *Bacillus subtilis*, compounds **6d**, **6g**, **6h** and **6l** were found to highly potent upon comparison with standard antibiotics. Towards *Salmonella typhi*, compounds **6d** and **6l** have shown outstanding inhibitory effect, while compounds **6d** and **6h** displayed strong inhibition against *Escherichia coli* as compared to the standard drugs. Antifungal study revealed that all the synthesized derivatives have poor activity against *Aspergillus fumigatus* except **6f**. In comparison with standard fungicidal griseofulvin, compounds **6d**, **6h** and **6l** were found to posses better inhibitory results towards *Candida albicans*. The encouraging results from the antimicrobial studies impelled us to go for preliminary screening of synthesized compounds against *Mycobacterium tuberculosis* H37Rv, which is summarized in Table 1. *In vitro* antituberculosis activity of all the newly synthesized compounds against *M. tuberculosis* H37Rv strain was determined by using Lowenstein–Jensen medium (conventional method) as described by Rattan [28]. Four compounds those exhibited highest % inhibition were again screened to get their MIC values (Table 1). Majority of the compounds displayed poor activity while compounds **6h** and **6l** showed best activity against *M. tuberculosis* H37Rv.

The structure–activity relationship (SAR) study indicates that a change in the substituent might also affect the antimicrobial activity of title compounds **6a–l**. It is interesting to point out, those compounds **6d**, **6h** and **6l** carrying electron negative groups on quinoline ring displayed excellent antimicrobial activity along with antituberculosis activity against majority of tested bacterial, fungal and tubercular strains.

Reviewing and comparing the activity data, it is worthy to mention that the compounds **6h** and **6l** emerged as the promising antimicrobial member with better antitubercular activity. Iodine catalyzed multi component reaction is proven synthetically useful to synthesize biologically active hybrid heterocyclic derivatives which is really non tedious and effective way to prepare active molecule's library against infectious disease. For full characterization, general procedure for the synthesis of title compounds and method for determination of *in vitro* biological activity see supporting information.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.cclet.2012.11.007.

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[26] Analytical data, **6h**: Yield 84%; mp 254 °C; MS *m/z*: 514.0 $[M+H]^+$; IR (KBr, cm^{-1}): 3000 (Ar. C–H str.), 1580 (C=C str.), 1660 (C=N str.), 745 (C–Cl str.); ^1H NMR (400 MHz, $CDCl_3$): δ 2.35 (s, 3H, CH_3), 6.80–8.55 (m, 18H, Ar–H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.07 (CH_3), 116.90, 117.23, 123.62, 126.90, 127.75, 128.10, 128.53, 128.66, 129.04, 129.30, 129.69, 130.42, 130.85, 131.32, 131.92, 132.40, 133.43, 133.87, 134.25, 135.26, 138.13, 139.67, 141.87, 146.65 (Ar–C); Anal. Calcd. for $C_{31}H_{21}ClN_6$: C 72.58, H 4.12, N 16.38 (%); Found: C 72.43, H 4.27, N 16.50 (%). **6l**: Yield 80%; mp 264–65 °C; MS *m/z*: 529.9 $[M+H]^+$; IR (KBr, cm^{-1}): 3010 (Ar. C–H str.), 1590 (C=C str.), 1610 (C=N str.), 740 (C–Cl str.), 1250 and 1040 (C–O–C asym. and sym. str. of $–OCH_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 3.67 (s, 3H, OCH_3), 6.62–8.59 (m, 18H, Ar–H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.25 (OCH_3), 113.97, 118.29, 124.78, 127.02, 127.35, 128.16, 128.53, 128.58, 128.94, 129.20, 129.64, 130.21, 131.01, 131.93, 132.51, 133.26, 133.40, 133.97, 134.18, 138.52, 140.85, 143.47, 146.30, 159.37 (Ar–C); Anal. Calcd. for $C_{31}H_{21}ClN_6O$: C 70.38, H 4.00, N 15.88 (%); Found: C 70.51, H 3.72, N 16.02 (%).
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