Anti HIV-1 Agents 6. Synthesis and Anti-HIV-1 Activity of Indolyl Glyoxamides

Yi Wang[a,#], Ning Huang[b,c,#], Xiang Yu[a], Liu-Meng Yang[b], Xiao-Yan Zhi[a] and Yong-Tang Zheng*[,b] and Hui Xu*[,a]

[a]*Laboratory of Pharmaceutical Design & Synthesis, College of Sciences, Northwest A&F University, Yangling 712100, P. R. China*

[b]*Key Laboratory of Animal Models and Human Diseases Mechanisms of Chinese Academy of Sciences and Yunnan Province, Kunming Institute of Zoology, Chinese Academy of Sciences, Kunming, Yunnan 650223, P. R. China*

[c]*Graduate School of the Chinese Academy of Sciences, Beijing 100039, P. R. China*

Abstract: In order to discover compounds with superior anti-human immunodeficiency virus type 1 (HIV-1) activity, 9 new indolyl glyoxamide derivatives (**3a-i**) were synthesized and preliminarily evaluated as HIV-1 inhibitors *in vitro*. Among all the derivatives, especially compounds **3e** and **3h** showed the potent anti-HIV-1 activity with EC_{50} values of 6.83 and 4.35 μg/mL, and TI values of >27.15 and 49.45, respectively. It demonstrated that introduction of the substituent R^3 as the halogen atom and the position of R^3 were generally important to their activity.

Keywords: Indolyl glyoxamide, Acquired immunodeficiency syndrome, Human immunodeficiency virus-1, Inhibitor.

INTRODUCTION

Recently, we have found that diaryl ethers (**I**, Fig. **1**) showed the promising antifungal activity against phytopathogenic fungi *in vitro* [1]. In the meantime, indibulin (**II**, Fig. **1**) was identified as a tubulin inhibitor by exerting antitumor activity [2]. Nowadays, fragment-based lead discovery has emerged as a more rational and focused approach for molecular modification and drug design. Based on the above observations, and in continuation of our program aimed at the discovery and development of bioactive molecules [3-5], consequently, we designed a series of indolyl glyoxamide derivatives (**3**, Fig. **1**) by combining the diaryl ethers group with indolyl glyoxamine moiety. On the other hand, since the first case of acquired immunodeficiency syndrome (AIDS) was reported in 1981, the human immunodeficiency virus (HIV)/AIDS has always been a global health threat and the leading cause of deaths [6-11]. The rapid worldwide spread of AIDS, therefore, has prompted an intense research effort to discover new, selective and safe drugs for the treatment of HIV/AIDS. Especially Wang and co-workers described that indolyl glyoxamide piperazines showed the anti-HIV-1 activity [12]. In this paper, nine new indolyl glyoxamide derivatives (**3a-i**) were synthesized and preliminarily evaluated as HIV-1 inhibitors *in vitro*.

*Address correspondence to these authors at the Laboratory of Pharmaceutical Design & Synthesis, College of Sciences, Northwest A&F University, Yangling 712100, China; Tel: +86-(0)29-87091952; Fax: +86-(0)29-87091952; E-mails: orgxuhui@nwsuaf.edu.cn, zhengyt@mail.kiz.ac.cn
#These authors contributed equally to this work.

RESULTS AND DISCUSSION

Chemistry

Indolyl glyoxamide derivatives (**3a-i**) were prepared as depicted in Scheme **1** [13]. Benzylindoles (**1**) were firstly treated with oxalyl chloride in dichloromethane to furnish the glyoxylyl chlorides as intermediates (**4**), which were then allowed to react with phenoxy phenylamines (**2a** or **2b**) in the presence of triethylamine to afford **3a-i** in 21-74% yields. The structures of all the target compounds were well identified by ^{1}H NMR, MS, and m.p.

Biological Activity

Target compounds **3a-i** were evaluated for their inhibitory activity against HIV-1 replication in acutely infected C8166 cells *in vitro* according to the previously described method [3]. The assay results of **3a-i** were presented in Table **1**. Among all the derivatives, especially compounds **3e** and **3h** exhibited the potent anti-HIV-1 activity with EC_{50} values of 6.83 and 4.35 μg/mL, and TI values of >27.15 and 49.45, respectively. Meanwhile, preliminary structure-activity relationships (SAR) showed the following interesting characteristics: (1) In general, introduction of the phenoxy group on the *para* position led to the more potent compound than that bearing the one on the *ortho* position (**3b** *vs* **3g**). (2) Introduction of the substituent R^3 as the chloro atom on the *para* position would generally lead to the more potent compound than that bearing the chloro one on the *ortho* position (**3d** *vs* **3c**). For example, the EC_{50} and TI values of **3c** and **3d** were 47.12/9.50 μg/mL, and >4.28/>19.98, respectively (3). When R^1 was the cyano group, introduction of the substituent R^3 as the chloro atom could lead to the more potent compound

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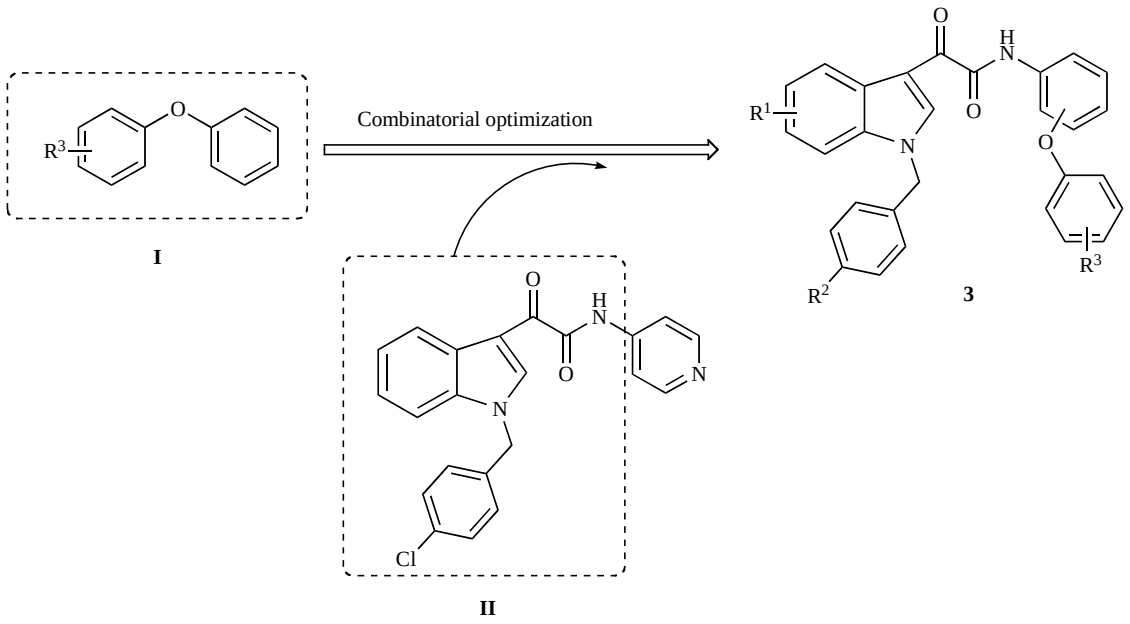
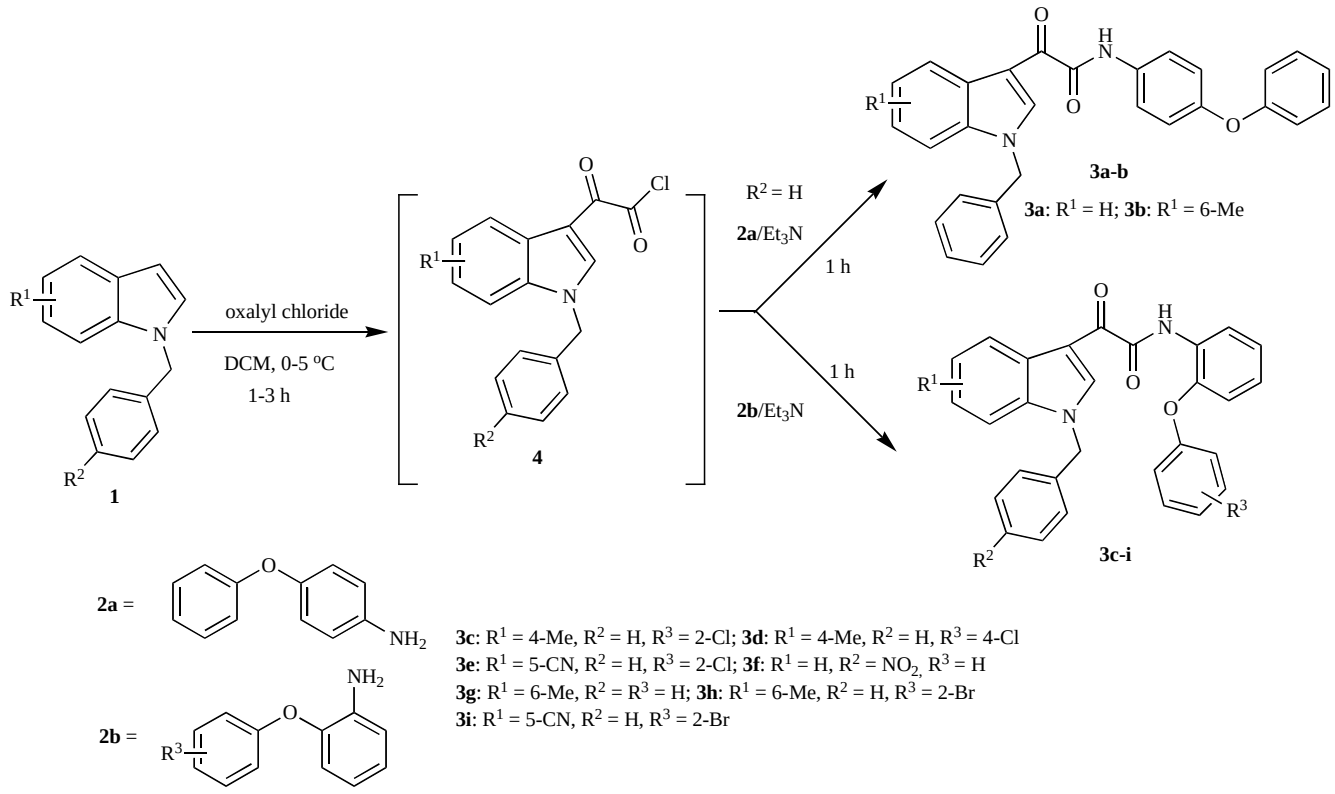


Fig. (1). Design Strategy of the Target Compounds **3**.



Scheme 1. Synthetic Route of **3a-i**.

than that bearing the bromo one (**3e** *vs* **3i**). For example, the cytotoxicity (CC_{50}), EC_{50} and TI values of **3e** and **3i** were >185.46/26.07 μg/mL, 6.83/10.94 μg/mL, and >27.15/2.41, respectively. Obviously, the cytotoxicity of **3e** was more than sevenfold less than that of **3i**, while the TI values of **3e** was more than elevenfold more potent than that of **3i**. (4) When R^1 was the 6-methyl group, introduction of the substituent R^3 as the bromo atom gave the more potent compound than that having no substituent (**3h** *vs* **3g**). For example, the CC_{50} and TI values of **3h** and **3g** were 98.18/3.14 μg/mL, and 49.45/0.97, respectively.

CONCLUSION

In conclusion, we have reported 9 new indolyl glyoxamide derivatives (**3a-i**) evaluated as HIV-1 inhibitors *in vitro*. Among all the derivatives, especially **3e** and **3h** exhibited the potent anti-HIV-1 activity with EC_{50} values of 6.83

Table 1. Anti-HIV-1 Activity of Indolyl Glyoxamide Derivatives (3a-i) *in Vitro* [a]

Compound	CC_{50} [b] (μg/mL)	EC_{50} [c] (μg/mL)	TI[d]
3a	96.05	18.67	5.16
3b	>154.56	22.76	>6.79
3c	>200	47.12	>4.28
3d	>189.87	9.50	>19.98
3e	>185.46	6.83	>27.15
3f	9.58	1.50	7.97
3g	3.14	3.31	0.97
3h	98.18	4.35	49.45
3i	26.07	10.94	2.41
AZT[e]	1730.28	0.00335	516,501.49

[a]Values are means of two separate experiments.
[b]CC_{50} (50% cytotoxic concentration), concentration of drug that causes 50% reduction in total C8166 cell number.
[c]EC_{50} (50% effective concentration), concentration of drug that reduces syncytia formation by 50%.
[d]Therapeutic Index (TI) is a ratio of the CC_{50} value/EC_{50} value.
[e]AZT was used as a positive control.

and 4.35 μg/mL, and TI values of >27.15 and 49.45, respectively. It demonstrated that introduction of the substituent R^3 as the halogen atom and the position of R^3 were generally important to their activity.

CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflicts of interest.

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REFERENCES

[1] Xu, H.; Jian, K.Z.; Guan, Q.; Ye, F.; Lv, M. Antifungal activity of some diaryl ethers. *Chem. Pharm. Bull.*, **2007**, *55*, 1755-1757.

[2] Bacher, G.; Nickel, B.; Emig, P.; Vanhoefer, U.; Seeber, S.; Shandra, A.; Klenner, T.; Beckers, T. D-24851, a novel synthetic microtubule inhibitor, exerts curative antitumoral activity *in vivo*, shows efficacy toward multidrug-resistant tumor cells, and lacks neurotoxicity. *Cancer Res.,* **2001**, *61*, 392-399.

[3] Fan, L.L.; Liu, W.Q.; Xu, H.; Yang, L.M.; Lv, M.; Zheng, Y.T. Anti HIV-1 agents 2. Discovery of dibenzofurans as new HIV-1 inhibitors *in vitro*. *Lett. Drug Des. Discov*., **2009**, *6*, 178-180.

[4] Huang, N.; Wang, Q.; Yang, L.M.; Xu, H.; Zheng, Y.T. Anti HIV-1 agents 7. Discovery of 1-hydroxy-4-chloro-9,10-anthraquinone derivatives as new HIV-1 inhibitors *in vitro*. *Lett. Drug Des. Discov*., **2011**, *8*, 602-605.

[5] Ran, J.Q.; Huang, N.; Xu, H.; Yang, L.; Lv, M.; Zheng, Y.T. Anti HIV-1 agents 5: Synthesis and anti-HIV-1 activity of some *N*-arylsulfonyl-3-acetylindoles *in vitro*. *Bioorg. Med. Chem. Lett.*, **2010**, *20*, 3534-3536.

[6] de Clercq, E. New developments in anti-HIV chemotherapy. *Biochim. Biophy. Acta*, **2002**, *1587*, 258-275.

[7] Lv, M.; Xu, H. Dipyridodiazepinone analogs as human immunodeficiency virus type 1-specific non-nucleoside reverse transcriptase inhibitors. *Curr. Med. Chem*., **2010**, *17*, 1874-1898.

[8] Johnston, M.I.; Hoth, D.F. Present status and future prospects for HIV therapies. *Science*, **1993**, *260*, 1286-1293.

[9] Kaushik, S.; Gupta, S.P.; Sharma, P.K.; Anwar, Z. A QSAR study on some series of HIV-1 integrase inhibitors. *Med. Chem*., **2011**, *7*, 553-560.

[10] Mitrasinovic, P.M.; Tomar, J.S.; Nair, M.S.; Barthwal, R. Modeling of HIV-1 TAR RNA-ligand complexes. *Med. Chem*., **2011**, *7*, 301-308.

[11] Ferreira, L.G.; Leitao, A.; Montanari, C.A.; Andricopulo, A.D. Comparative molecular field analysis of a series of inhibitors of HIV-1 protease. *Med. Chem*., **2011**, *7*, 71-79.

[12] Wang, T.; Kadow, J.F.; Zhang, Z.; Yin, Z.; Gao, Q.; Wu, D.; Parker, D.D.; Yang, Z.; Zadjura, L.; Robinson, B.A.; Gong, Y.; Blair, W.S.; Shi, P.; Yamanaka, G.; Lin, P.; Meanwell, N.A. Inhibitors of HIV-1 attachment. Part 4: A study of the effect of piperazine substitution patterns on antiviral potency in the context of indole-based derivatives. *Bioorg. Med. Chem. Lett.,* **2009**, *19*, 5140-5145.

[13] Roy, S.; Eastman, A.; Gribble, G.W. Synthesis of *N*-alkyl substituted bioactive indolocarbazoles related to Gö6976. *Tetrahedron,* **2006**, *62*, 7838-7845.

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